EPA Reg. No. 11556-126
Vol. 1

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

JAN 13 2003

Mr. F. Terry McNamara
Bayer Corporation
Animal Health, Agriculture Division
P. O. Box 390
Shawnee Mission, KS 66201

Subject: CRP Testing for New Advantage Products

Advantage Plus 9	11556-REA
Advantage Plus 10	11556-REI
Advantage Plus 20	11556-REL
Advantage Plus 18	11556-REO
Advantage Plus 55	11556-RET
Advangage Plus 100	11556-RGN

Your Submission date, November 13, 2002

Dear Mr. McNamara:

The Agency has received and reviewed your Child Resistant Packaging (CRP) study protocol for all six of the above listed products. After careful review, there are a number of questions/clarifications concerning the testing protocols. A copy of the results are attached. Please review the results and resubmit in accordance with the directions given by Dr. Gross. If I can be of assistance in anyway, call me at 703 305-5409.

Sincerely,

/s/

Dani Daniel
Insecticide/Rodenticide Branch
Registration Division 7505C

Attachment:

CHILD-RESISTANT PACKAGING REVIEW
Technical Review Branch

IN 12/03/02 OUT 12/11/02

Reviewed by Rosalind L. Gross 12/11/02

EPA Reg. No. or File Symbol 11556-REA,11556-REI, 11556-REL, 11556-RET, 11556-RGN, 11556-REO

DP Barcode D287000, D287001, D287003, D287004, D287005, D287006

EPA Petition or EUP No. _____

Date Division Received 11/18/02

Type Product(s) Insecticide

Data Accession No(s). _____

Product Mgr./Chemical Review Mgr/Contact Person PM 04 (Helen Daniel)
Division RD

Product Name(s) Advantage Plus 9 for Cats, Advantage Plus 10 for Dogs, Advantage Plus 20 for Dogs, Advantage Plus 55 for Dogs, Advantage Plus 100 for Dogs, Advantage Plus 18 for Cats

Company Name(s) Bayer Corp

Submission Purpose Review protocol testing scheme for child-resistant effectiveness test and senior adult use effectiveness test along with other requirements to fulfill CRP requirements for this product

Active Ingredient(s), PC code, & % Imidacloprid 9.1%

Summary

The child resistant effectiveness and senior adult use effectiveness test protocols submitted for these 6 products resulted in a number of questions/clarifications regarding the product such as what was the actual child-resistant package (CRP), what was the definition of a child failure, etc. The result was a telephone conference call on 12/5/02 with the registrant and the CRP testing organization (see attached questions/clarifications) and a 12/9/02 follow-up telephone call between Rosalind L.

Gross, EPA and Dr. Harish Chopade, Bayer. The conclusion of the aforementioned conversations and the review of the child resistant effectiveness and senior adult use effectiveness test protocols submitted for these 6 products is that **either the blister or the tube itself must be child-resistant. All three size tubes and both package sizes for each tube size must be tested. The exception** is the 1 ml or less tube size requires CRP only if at least 9 tubes are in a retail package. However, **unless** the packaging for the **one ml or less tube sizes is in a different package (not just a different color), but a different design/style than the CRP sizes it will also have to be tested. A bracketing scheme with prior Agency approval is suggested.**

A new submission with a **testing scheme for the three tube sizes and the two package sizes should be approved prior to testing.** Samples of the package to be used for CRP testing must be provided. For the CRP requirements for this product to be met the data for the child resistant effectiveness and senior adult use effectiveness tests must be submitted both electronically in accordance with PR 97-9 and a hardcopy, also a CRP certification needs to be submitted.

Some of the problems with the submission are:

1. The chart of the number of tubes representing a failure for child test submitted by the registrant is incorrect. This must be corrected.

2. Testing one tube size (4.0ml) in one package size (6 tubes) is insufficient. Potentially 6 packages need to be subjected to CRP testing. A bracketing scheme with prior Agency approval is suggested.

3. The tube itself or the blister must be the child-resistant package rather than a combination of the two being the child-resistant.

4. Note labeling indicating this is a single use tube must be provided to the Agency.

5. If the **blister** is the package tested for CRP: The children are given the number of blister cards that represent a toxic or harmful amount of product at the beginning of the test (e.g. 1 ml tube size or less 2 blister cards for access to at least 9 tubes). A **blister/package failure is access/potential to the tube**, the tube does not have to be physically removed from the blister or opened. If the **tube** is the package tested for CRP: The children are given the number of tubes that represent a toxic or harmful amount of product at the beginning of the test (e.g. 1 ml tube size or less access to at least 9 tubes with a maximum of 12 tubes). A **tube/package failure is access/potential to the contents of the tube in whole or in part**, which means even a pinhole size opening in the tube is a failure since the product is a liquid. A **child failure needs to be correctly defined in each test report** based on the tube size and the number of tubes

given to the child to represent a toxic or harmful amount in that test (e.g.1 ml tube size or less access to at least 9 tubes). **The package demonstration of how to open a package by the tester (child test protocol item 25) and the definition of a package failure (child test protocol item 30) need to be adjusted dependent on whether the blister or the tube is the CRP.**

6. If the **blister** is the package tested for CRP: The senior test needs to be modified to reflect the need only to remove the tube from the blister. A **package failure needs to be defined.** If the **tube** is the package tested for CRP: The senior test needs to be modified to reflect the need only to remove the product from the tube. A **package failure needs to be defined.**

Analysis of Data and Discussion

Product/Package Information

The registrant indicated the product is to be marketed in 3 tube sizes which are: one tube size for the 0.4, 0.8, and 1 ml, a second tube size for the 2.5 ml, and a third tube size for the 4.0ml. The product is to be marketed for all three tube sizes in a 4 tube package and a 6 tube package. **Testing one tube size (4.0ml) in one package size (6 tubes) is insufficient.** Potentially 6 packages need to be subjected to CRP testing. A bracketing scheme with prior Agency approval is suggested.

Based on toxicity the tube size for 1 ml or less requires CRP only if at least 9 tubes are in a retail package. However, **unless** the packaging for the **one ml or less tube sizes is in a different package (not just a different color), but a different design/style than the CRP sizes it will also have to be tested.** This requirement is based on the fact that using the same package for all three tube sizes constitutes voluntary use of CRP, which per 40 CFR 157.30 is required to meet the same standards as mandatory CRP.

The package for each of the tube sizes and package sizes consists of a single use tube in a blister package. For the dog products the blister package is then placed in an outer cardboard carton, for the cat products the blister package is placed on a cardboard card. **The tube itself or the blister must be the child-resistant package rather than a combination of the two being the child-resistant.** The rationale for this statement is that the tube is the immediate package and the blister is once removed from the immediate package. Both the blister and the outer cardboard carton (in the case of dog products) are considered to be secondary packaging. 40 CFR 157.27 Unit packaging allows for either the unit package (the tube in this instance) or the outer package (the blister in this instance) to be CRP. **Note labeling indicating this is a single use tube must be provided to the Agency.**

Toxicity Data

The registrant indicated an oral LD_{50} of 1283 mg/kg in male rats and 1000mg/kg in female rats. Based on a worst case scenario the registrant decided to use the female rat oral LD_{50} of 1000mg/kg. The toxic or harmful amount of product for a 25 lb (11.4kg) child using the oral LD_{50} 1g/kg and product specific gravity of 1.092g/ml is 11.4g = 10.44ml. Based on the toxic or harmful amount of 11.4g or 10.44ml of product the number of tubes used for a failure based on tube size is as follows:

tube size (ml)	# of tubes a failure for child test
0.4	27 (therefore access to 9 tubes is a failure)
0.8	14 (therefore access to 9 tubes is a failure)
1.0	11 (therefore access to 9 tubes is a failure)
2.5	5
4.0	3

The chart of the number of tubes representing a failure for child test submitted by the registrant is incorrect. It must be corrected.

Child Test

If the **blister** is the package tested for CRP: The children are given the number of blister cards that represent a toxic or harmful amount of product at the beginning of the test (e.g. 1 ml tube size or less 2 blister cards for access to at least 9 tubes). A **blister/package failure is access/potential to the tube**, the tube does not have to be physically removed from the blister or opened. If the **tube** is the package tested for CRP: The children are given the number of tubes that represent a toxic or harmful amount of product at the beginning of the test (e.g. 1 ml tube size or less access to at least 9 tubes with a maximum of 12 tubes). A **tube/package failure is access/potential to the contents of the tube in whole or in part**, which means even a pinhole size opening in the tube is a failure since the product is a liquid. A **child failure needs to be correctly defined in each test report** based on the tube size and the number of tubes given to the child to represent a toxic or harmful amount in that test (e.g.1 ml tube size or less access to at least 9 tubes). The package demonstration of how to open a package by the tester (child test protocol item 25) and the definition of a

package failure (child test protocol item 30) need to be adjusted dependent on whether the blister or the tube is the CRP.

Senior Adult Use Effectiveness Test

If the **blister** is the package tested for CRP: The senior test needs to be modified to reflect the need only to remove the tube from the blister. A **package failure needs to be defined.** If the **tube** is the package tested for CRP: The senior test needs to be modified to reflect the need only to remove the product from the tube. A **package failure needs to be defined.**

Final Report and Addendum

When these studies are submitted both an electronic (per PR Notice 97-9) and hard copies must be submitted. The hard copy Final Report or an Addendum to it in addition to the requirements in 16 CFR 1700.20 should include:

A sample of the child-resistant blister card with the tube or the package to be tested.

Indicate how many tubes/blister cards the child got at the start of the test.

Report the **number of tubes/blisters each child accessed** not just whether or not it was a child failure.

Define a package failure.

Define a child failure.

Describe the Senior Adult Protocol used.

Define a Senior Adult test failure.

Include a copy of the instructions used in Senior Adult Use Effectiveness test.

Note any change in the color, composition, size,, etc. for the tube/blister from what was originally tested may necessitate retesting.

A CRP certification in accordance with 40 CFR Part 157 must be submitted. **Note** if any changes occur in the color, composition, size, etc. for the tube/blister from what was originally tested a new CRP certification is required and retesting may be required.

Conclusion

In conclusion, a new submission with a **testing scheme for the three tube sizes and the two package sizes should be approved prior to testing.** Samples of the package to be used for CRP testing must be provided. For the CRP requirements for this product to be met the data for the child resistant effectiveness and senior adult use effectiveness tests must be submitted both electronically in accordance with PR 97-9 and a hardcopy, also a CRP certification needs to be submitted.

All test samples from the child test panel and senior adult test panel should be retained at a minimum until after EPA has accepted the test data and CRP certification. If a question arises as to whether or not a failure exists EPA may ask for the test sample to be examined and a failure to do so could be problematic.

CRP Testing for Advantage Plus
EPA Reg. No. 11556-REA, 11556-REI, 11556-REL, 11556-RET, 11556-RGN, 11556-REO

There are a number of questions/clarifications that should accompany the CRP testing protocols before testing is undertaken. The child test panel and senior adult test panel are following the general procedures in 16 CFR 1700.20. However there are some details not in 16 CFR 1700.20 that need to be addressed in terms of what packages are tested and what type of information is seen in the written final study report. These questions/clarifications are as follows:

1. Product is to be marketed in tubes with 0.4, 0.8, 1.0, 2.5, and 4.0 ml of product. Will the actual physical size for each of these 5 tubes be different? If not, please indicate which product sizes (e.g. 0.4, 0.8, 1.0 ml) will be in the same physical size tube. This should be in the written final study report or in a cover letter accompanying it. Note each physical size tube will need to be tested and the data reviewed.

2. The product is to be marketed in a nonchild-resistant tube in a child-resistant blister card. Have I understood this correctly?

3. Each child-resistant blister card would contain 6 tubes. Are there any other blister card sizes (e.g. a 4 tube child-resistant blister card) planned for the present or the future? Each blister card size would have to be tested. This means 5 different physical size tubes in two different blister card sizes each would require 10 tests. Should some type of bracketing scheme be considered? Note testing the 4 ml size alone will not suffice. Were you planning to test other sizes?

4. Since the tube is nonchild-resistant, the labeling would have to support single use because once the tube is out of the blister it is no longer CRP.

5. According to the toxicity data presented the 0.4, 0.8, 1.0 ml sizes would define a child failure as access to 9 units of the blister card per 16 CFR 1700.20. If only 6 tubes of product are in child-resistant blister card, then that size is not subject to CRP (a toxic or harmful amount is not available). However, if all 5 sizes of product (0.4, 0.8, 1.0, 2.5, and 4.0 ml) use the same package then, the 0.4, 0.8, 1.0 ml sizes must be in CRP and each child would have to receive 12 tubes/2 blister cards at the beginning of the test so that a child has potential access to a toxic or harmful amount at the beginning of the test.

6. Why is a child being given a second blister card for the 4 ml product size test?

7. According to the toxicity data presented the 0.4, 0.8, 1.0 ml sizes would define a child failure as access to 9 units of the blister card per 16 CFR 1700.20. The definition

of a child failure as access to 9 units of the blister card for these product sizes should be in the written final study report. The definition of a child failure as access to 4 or 2 units of the blister card for the 2.5 and 4ml product sizes should be in the written final study report.

8. Since the tube is nonchild-resistant and the blister card is the child-resistant feature an opening or blister failure would be opening the blister such that the tube is available. The child would not have to do anything to the tube for it to be a failure. Why have you stated it as involving the tube in item 30 page 7? There should be agreement between EPA and Bayer as to what "opening the blister such that the tube is available" means before testing. Digital photos as a jpg file of the definition of a blister failure pretesting would be good.

9. Records should be kept of the number of tubes accessed per child in each 5 minute period and for the full 10 minutes. Will this be done?

10. What does a sample of the child-resistant blister card with the tube look like? Please send a physical sample.

11. Will the test data be formatted in accordance with PR97-9, since it will have to be submitted for review electronically as well as written format?

12. All test samples from the child test panel and senior adult test panel should be retained at a minimum until after EPA has accepted the test data and CRP certification. If a question arises as to whether or not a blister failure exists EPA may ask for the test sample to be examined and a failure to do so could be problematic.

13. For the senior adult test panel will the participant be given a blister, asked to open it, remove one tube, and squirt a small amount into something? If so the opening of the blister and removal of the tube should be specified in the written final study report. A copy of the instructions given to the seniors should be in the written final study report or in a cover letter accompanying it. The company would have to include these instructions in the package labeling approved for marketing.

PM

Bayer

Agriculture Division

Animal Health

Bayer Corporation
P.O. Box 390
Shawnee Mission, KS 66201-0390
Phone: 913 268-2000

November 13, 2002

Ms. Dani Daniel
7505C
USEPA Headquarters
Ariel Rios Building
1200 Pennsylvania Avenue, N.W.
Washington, D.C. 20460

Subject: Final Registration Requirement for Advantage® Plus 9, 18, 10, 20, 55, and 100 products (EPA File Symbols 11556-REO, -REA, -REI, -REL, -RET, -RGN)

Dear Ms. Daniel,

Bayer Animal Health has Applications for Registration for the above reference products pending with the Agency. Bayer has fulfilled all of the requirements need for registration including Product Chemistry (EPA Letter dated 1/12/02, Bayer response dated 4/12/01), Acute Toxicology (EPA letter dated 9/7/00), and Domestic Animal Safety (EPA letter dated 10/5/00). Therefore, the final data requirement needed to obtain registration is Child Resistant Packaging (CRP) testing.

A protocol for CRP testing was developed based on a meeting between EPA and Bayer held on April 21, 2001 which you attended. We would like Dr. Rosalind Gross, the primary technical reviewer for CRP requirements, to review our study protocol prior to initiating the CRP testing.

The study protocol has been developed and copies are enclosed for Dr. Gross's review. In a recent communication with our CRP testing consultant (Dr. Lori Dixon), Dr. Gross requested that we submit the protocol to her via the Registrations Division. Since you are the registration person for the above referenced products, enclosed are two copies of the protocol – one for your files and one for you to forward to Dr. Gross. Once we receive comments from Dr. Gross, the study protocol will be modified (if needed) and the study initiated. The final study report will be sent to you as soon as it is available.

Please call me at 913-268-2588 or Mr. Greg Gagliano at 913-268-2751 if you have any questions or need additional information. Thank you very much for your assistance and consideration in handling this request.

Sincerely,

F. Terry McNamara

F. Terry McNamara
Director, Preclinical Development and EPA Regulatory Affairs

FTM:GGG/lt

Enclosures

PM
Copy

Bayer Animal Health – Protocol for "Child-Resistant Packaging Test for Imidaclorpid (9.1%)/Pyriproxyfen (0.46%) for Dogs and Cats"

STUDY PROTOCOL

Study Title: Child-Resistant Packaging Test for Imidaclorpid (9.1%)/ Pyriproxyfen (0.46%) for Dogs and Cats

Reference: 40 CFR Part 157.20 and 16 CFR Part 1700.20

GLP Study: No

Study Director:
L. M. Dixon, Ph.D.
Great Lakes Marketing
3103 Executive Parkway, Suite 106
Toledo, OH 43606-1211
Phone: (419) 534-4700; Fax: (419) 531-8950

Sponsor:
Bayer Animal Health
PO Box 390, Shawnee Mission, Kansas 66201
Phone: (913) 268-2509; Fax: (913) 268-2135

Sponsor Representative.:
H. M. Chopade, Ph.D.
Manager, Metabolism and Residue
Preclinical Development & EPA Regulatory Affairs
Research and Development, Bayer Animal Health

Project No.: 10342

Study No.: 151.367

Proposed Dates: Start Date: 11/2002; End Date: 02/2003

Signatures:

L. M. Dixon, Ph.D. Study Director, Great Lakes Marketing	Date
H. M. Chopade, Ph.D. Manager, Metabolism and Residue Preclinical Development and EPA Regulatory Affairs	Date
F. T. McNamara, M.S. Director, Preclinical Development and EPA Regularoty Affairs	Date

Bayer Animal Health – Protocol for "Child-Resistant Packaging Test for Imidaclorpid (9.1%)/Pyriproxyfen (0.46%) for Dogs and Cats"

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Bayer Animal Health – Protocol for "Child-Resistant Packaging Test for Imidaclorpid (9.1%)/Pyriproxyfen (0.46%) for Dogs and Cats"

STUDY PROTOCOL

Introduction and Purpose: The packaging requirements for pesticides and devices to be marketed in the United States are prescribed in Code of Federal Regulations, 40 CFR Part 157.20. Bayer Animal Health is developing Advantage Plus, a product containing 9.1% imidacloprid and 0.46% pyriproxyfen for dogs and cats. The product is to be marketed in tubes of four different sizes, 0.4, 0.8, 1.0, 2.5, and 4.0 mL. The tubes will be packaged in blisters; each blister will contain 6 tubes. The acute oral LD_{50} for this product was determined to be 1,283 mg/kg for male and 1,000 mg/kg for female rats.[1] This product meets the US EPA 40 CFR Part 157.22 requirements for child-resistant packaging according to the following toxicity criteria:
(1) Toxicity criterion – the pesticide has an oral LD_{50} of 1.5 g/kg or less and
(2) Use criterion – The product's labeling either directly recommends residential use or reasonably can be interpreted to permit residential use.

The number of tubes of this product a child weighing 25 pounds (11.4 kg) would have to ingest to reach a toxic dose are provided in the table below. "Toxic dose" for this product as defined in 40 CFR Part 157.22 and that confirmed by Dr. Rosalind Gross of US EPA is the acute oral LD_{50} value. Thus, to err on the conservative side, the LD_{50} value of 1,000 mg/kg for female rats was used in the supporting calculations. The specific gravity of the product, 1.092 g/mL, was also used in the supporting calculations.

Advantage Plus Tube Size (ml)	No. of Tubes Constitute as Toxic Dose to a Child
0.4	26
0.8	13
1.0	10
2.5	4
4.0	2

The purpose of this study is to evaluate the child-resistant packaging of two types: (1) Advantage type blister pack with 0.02 mm aluminum foil, and (2) Improved Advantage type blister pack with 0.03 mm aluminum foil. These two blister types are currently being considered as a potential packaging for a new product, Advantage Plus, containing 9.1% imidacloprid and 0.46% pyriproxyfen for dogs and cats. The child-resistant packaging test will be conducted with only 4-mL tubes for each type of blister pack. The 4.0 mL tube size represents the largest of the five tube sizes to be used for the new product. At the start of the test, the 4-mL Advantage type blister packs will be tested. If these blisters do not pass in the initial child test, the senior adult panel testing will not be performed. The next test will begin with 4-mL Improved Advantage type blister packs. The Child Panel Test and Senior Adult Panel Test protocols to be used for this child-resistant packaging test are presented on the

following pages. The results of these tests will be evaluated to determine whether these two types of packaging can meet the effectiveness specifications given in 16 CFR Part 1700.15(b) for child-resistant (special) packaging needed for Imidaclorpid (9.1%)/ Pyriproxyfen (0.46%), a new Bayer Animal Health product for dogs and cats.

Study Director: Dr. L. M. Dixon at Great Lakes Marketing will serve as the Study Director for this project. The address for Great Lakes Marketing is 3103 Executive Parkway, Suite 106, Toledo, OH 43606-1211; Phone: (419) 534-4700; Fax: (419) 531-8950). Dr. Dixon is experienced in conducting the child-resistant packaging tests with pesticides, devices, and drugs. Dr. Harish Chopade, Manager, Metabolism and Residue in the Preclinical Development and EPA Regulatory Affairs Group (Animal Health, Shawnee, Kansas) will serve as the Sponsor Representative. The Study Director will be responsible for: (1) writing the study protocol, (2) overall conduct of the study, (3) writing and/or approval of study protocol deviations/amendments in consultation with the Sponsor Representative (4) interpretation and analysis of the results, (5) writing the final study report. This non-GLP study will be performed in a scientific and professional manner, and all necessary observations and documentation for the study will be obtained and maintained in the spirit of EPA's Good Laboratory Practice Standards (GLP; 40 CFR Part 160).

Quality Assurance: The Study Director, Dr. L. M. Dixon, will be responsible for the quality and data integrity of the research project.

Sample Shipment and Storage: There are no special storage requirements for the test packaging to be used in this test. The test samples will be shipped via UPS ground carrier at ambient temperature to the Great Lakes Marketing, Toledo, OH, where they will be maintained at the room temperature. The storage conditions of the test samples will be documented in the test data files.

Records to be Maintained: Upon the completion of the final report, the signed report and all original raw data of the tests and related documents will be transferred from Great Lakes Marketing to Bayer Animal Heath, PO Box 390, Shawnee Mission, Kansas 66201 for permanent archive and storage.

Bayer Animal Health – Protocol for "Child-Resistant Packaging Test for Imidaclorpid (9.1%)/Pyriproxyfen (0.46%) for Dogs and Cats"

Child Panel Test Protocol

The following Child Panel Test Protocol follows the procedure stated in the Federal Register, Title 16, Part 1700.20.

1. Client will provide XXX cards (all from Lot Number xxxx).

2. Calendars, stickers, and other materials that are removed by the consumer in the normal use of the product will be removed before testing begins.

3. The cards will contain six tubes; each housed in an individual blister.

4. Each tube will contain 4.0 mL of distilled water instead of a placebo.

5. No opening directions will be presented on the tubes. The blister cards will be immediately accessible to the children and will not be housed in any additional shelf packaging.

6. All cards will be handled so that no damage would occur during storage or transportation. The cards will not be exposed to extreme conditions of heat or cold. The cards will be tested at room temperature.

7. The children used for this test will have no overt physical or mental handicaps. No child with a permanent or temporary illness, injury, or handicap that could interfere with his/her effective participation will be included in the test.

8. The testing will take place in a well-lighted location that is familiar to the children and that is isolated from all distractions.

9. The tester, or another adult, will escort a pair of children to the test area. The tester will place the two so that there will be no visual barrier between the children and the tester.

10. The tester will talk to the children to make them feel at ease.

11. The children will not be given the impression that they are in a race or contest. They will not be told that the test is a game or that it is fun. They will not be offered a reward.

12. The tester will record all data prior to or after, the test so that full attention can be on the children during the test period.

Child Panel Test Protocol (cont.)

13. The tester will use a stopwatch(s) to record the number of seconds it takes the child to open each tube and to time the five-minute test periods.

14. To begin the test, the tester will hand **one card** to each child and say, "*PLEASE TRY TO OPEN THIS FOR ME.*"

15. If a child refuses to participate after the test has started, the tester will reassure the child and gently encourage the child to try. If the child continues to refuse, the tester will ask the child to hold the package in his/her lap until the other child is finished. The pair of children will not be eliminated from the results unless the refusing child disrupts the participation of the other child.

16. Each child will be given up to five minutes to open his/her tubes. The tester will watch the children at all times during the test. The tester will minimize conversation with the children as long as they continue to attempt to open their packages. The tester will not discourage the children verbally or with facial expressions. If a child gets frustrated or bored and stops trying to open his/her package, the tester will reassure the child and gently encourage the child to keep trying.

17. The children will be allowed freedom of movement to work on their packages as long as the tester is able to watch both children (e.g., they can stand up or bang or pry the package).

18. If a child is observed endangering himself or others at any time, the test will be stopped and the pair of children eliminated from the final results.

19. The children will be allowed to talk to each other about opening the packages and will be allowed to watch each other try to open the packages.

20. A child will not be allowed to try to open the other child's package.

21. If a child opens his/her package, the tester will say, "THANK YOU," and take the package from the child and put it out of the child's reach. **The child will then be given a second card.** The child will be asked to stay until the other child finishes.

22. At the end of the five-minute period, the tester will demonstrate how to open the package if either child has not opened their package. A separate "demo" package, identical to the child's package, is used for the demonstration. The tester uses a new package for each demonstration.

Child Panel Test Protocol (cont.)

23. Prior to beginning the demonstration, the tester will ask each of the children to hold their package still or set the packages aside. The children will not be allowed to continue to try to open their packages during the demonstration period.

24. The tester will say, "*WATCH ME OPEN MY PACKAGE.*"

25. Once the tester secures the children's full attention, he/she will hold the demo package approximately two feet from the children and will open the package at a normal speed as if he/she will be using the contents. There will be no exaggerated opening movements. To perform the demonstration, the tester will hold the package with the front of the package facing the children. The tester will remove one tube from the card, put the card down, and then open the tube. After opening the tube, the tester will replace the cap on the tube.

26. The tester will not discuss or describe how to open the package. The demonstration will be visual only.

27. To begin the second five-minute period, the tester will say, "NOW YOU TRY TO OPEN YOUR PACKAGE."

28. If one or both children have not used their teeth to try to open their packages during the first five minutes, the tester will immediately say before beginning the second five-minute period, "YOU CAN USE YOUR TEETH IF YOU WANT TO." This will be the only statement that the tester makes about using teeth.

29. The test will continue for an additional five minutes or until both children have opened their package, whichever comes first.

30. An opening will be defined as penetrating the foil on the top of the tube. Each tube that is opened will be recorded. **If a child opened two 4-mL tubes, it will be considered a failure.**

31. At the end of the test period, the tester will say, "THANK YOU FOR HELPING." If children were told to use their teeth, the tester will say, "I KNOW I TOLD YOU THAT YOU COULD USE YOUR TEETH TODAY, BUT YOU SHOULD NOT PUT THINGS LIKE THIS IN YOUR MOUTH AGAIN." In addition, the tester will say, "NEVER OPEN PACKAGES LIKE THIS WHEN YOU ARE BY YOURSELF. THIS KIND OF PACKAGE MIGHT HAVE SOMETHING IN IT THAT WOULD MAKE YOU SICK."

32. The children will be escorted back to their classroom, or other supervised area, by the tester or another adult.

Bayer Animal Health – Protocol for "Child-Resistant Packaging Test for Imidaclorpid (9.1%)/Pyriproxyfen (0.46%) for Dogs and Cats"

Senior Adult Panel Test Protocol

Adults who did not successfully open one child-resistant tube [referred to as package] during the first five-minute time period will be asked to attempt to open and resecure two conventional (non-child resistant) packages:

1. An 8 dram (+/- 4 drams) round plastic package with a 28 mm (+/- 18%) non-child resistant snap closure.

2. A 2 ounce (+/- 1/2 ounce) round plastic package with a 28 mm (+/- 18%) non-child resistant continuous threaded closure. The closures resecured to 10 torque inch-pounds at least 72 hours before testing.

Test Procedures

1. The following test protocol follows that written in the Federal Register, Title 16, Part 1700.20 for Senior Adults.

2. All packages will be handled so that no damage or jarring will occur during storage or transportation. The packages will not be exposed to extreme conditions of heat or cold. The packages will be tested at room temperature.

3. The adults with no overt physical or mental handicaps will be selected for the test. No adult with a permanent or temporary illness, injury or handicap that would interfere with his/her effective participation will be included in the test.

4. Before beginning the test, the tester will say, "PLEASE READ AND SIGN THIS CONSENT FORM." Adults who failed to read the consent form for any reason (forgot glasses, illiterate, etc.) will not participate in the test.

5. Each adult will participate individually and not in the presence of other participants or onlookers.

6. The test area will be well-lighted and free from distractions.

7. Records will be filled in prior to or after, the test so that the tester's full attention will be on the participant during the test period. The only exception will be to record the test times to open and close the package.

8. XXX cards (all from Lot Number xxx) will be received from the client. Calendars, stickers and other materials that would be removed by the consumer in the normal use of the product will be removed before testing began.

Senior Adult Panel Test Protocol (cont.)

9. To begin the first five-minute test period, the tester will say, "I AM GOING TO ASK YOU TO OPEN THESE TWO IDENTICAL PACKAGES ACCORDING TO THE INSTRUCTIONS ON THIS PAPER."

10. The tester will give the participant a package and opening directions and say, "PLEASE OPEN THIS PACKAGE ACCORDING TO THE INSTRUCTIONS." After the participant opened the package, the tester will say, "PLEASE SQUIRT A SMALL AMOUNT INTO THIS CUP."

11. The participant will be allowed up to five minutes to read the instructions and open the package. The tester will use a stopwatch(s) or other timing device to record the opening times. The elapsed time in seconds to open the package will be recorded on the data sheet.

12. After five minutes or when the participant has opened the package, whichever came first, the tester will take all test materials from the participant. If a participant did not open a package and stopped trying to open it by the end of the first five-minute period, the tester will say, "ARE YOU FINISHED WITH THE PACKAGE OR WOULD YOU LIKE TO TRY AGAIN?" If the participant indicated that he/she is finished or could not open the package and would not wish to continue trying, the participant will be asked to open and close two screening packages. The adult participant will be given a one-minute test period for each package. The tester will give the participant a package and will say, "PLEASE OPEN AND PROPERLY CLOSE THIS PACKAGE." The tester will record the time for opening and closing or one minute, whichever is less, on the data sheet. The tester then will give the participant the second package and will say, "PLEASE OPEN AND PROPERLY CLOSE THIS PACKAGE." The time to open and resecure or one minute, whichever is less, will be recorded on the data sheet. Any participant who could not open and resecure both of the non-child resistant screening packages will not be counted as part of the 100 adult panel. Additional adults will be selected and tested.

13. To begin the second test period, the tester will give the participant a NEW package and say, "PLEASE OPEN THIS PACKAGE." After the participant opened the package, the tester will say, "PLEASE SQUIRT SOME WATER INTO THIS CUP."

14. The participant will be allowed up to one minute to open the package. The elapsed time in seconds to open the package will be recorded on the data sheet.

15. After one minute or when the participant will have opened the package, whichever came first, the tester will take all test materials from the participant. If a participant did not open a package and stopped trying to open it by the end of the one-minute test period, the

Senior Adult Panel Test Protocol (cont.)

tester will say, "ARE YOU FINISHED WITH THE PACKAGE OR WOULD YOU LIKE TO TRY AGAIN?" If the participant indicated that he/she is finished or could not open the package and would not wish to continue trying, this will be counted as a failure of the one-minute test. No adult will participate in more than two tests per sitting. If a person has participated in two tests, the packages tested would not be the same type of package.

REFERENCE

1. Sturdivant, D.W. 1999. Acute oral LD_{50} toxicity study with imidacloprid (9.1%)/pyriproxyfen (0.9%) spot-on in rats, Bayer Animal Health Report No. 75195, MRID No. 45096904.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

JAN 12 2001

Mr. F. Terry McNamara
Bayer Corporation
Animal Health, Agriculture Division
P.O. Box 390
Shawnee Mission, KS 66201

Subject: Applications for New Advantage Products
Reg. No. 11556-REA, REO, REI, REL, RET, RGN
Your submission date, April 7, 2000

Dear Mr. McNamara:

The labeling referred to above, submitted in connection with the above registrations under the Federal Insecticide, Fungicide, and Rodenticide Act have been reevaluated based on the additional information given, however, there are a number of things that the Agency insist upon and Bayer must comply but registration will be issued.

Enclosed are the conclusions issued by the Product Chemistry Branch. Please read the review and make changes as specified. Upon making the changes, please resubmit your labels and CSFs. If there are question, call me at 703 305-5409.

Sincerely,

Dani Daniel
Insecticide-Rodenticide Branch
Registration Division 7505C

Enclosure:

DATE: 22/NOV/2000

SUBJECT: PRODUCT CHEMISTRY REVIEW OF MP [ ] EP's [X]

DP BARCODE No.: D270181
REG./File Symbol No.: 11556-REA
PRODUCT NAME: Advantage Plus 9 for Cats
AND
DP BARCODE No.: D270183
REG./File Symbol No.: 11556-REI
PRODUCT NAME: Advantage Plus 10 for Dogs
AND
DP BARCODE No.: D270184
REG./File Symbol No.: 11556-REL
PRODUCT NAME: Advantage Plus 20 for Dogs
AND
DP BARCODE No.: D270182
REG./File Symbol No.: 11556-REO
PRODUCT NAME: Advantage Plus 18 for Cats
AND
DP BARCODE No.: D270186
REG./File Symbol No.: 11556-RET
PRODUCT NAME: Advantage Plus 55 for Dogs
AND
DP BARCODE No.: D270188
REG./File Symbol No.: 11556-RGN
PRODUCT NAME: Advantage Plus 100 for Dogs

← FILE

COMPANY: Bayer Corporation

FROM: Linda L. Kutney, Chemist
Product Chemistry Team
Technical Review Branch (TRB)/RD (7505C)

Linda L Kutney 11-22-00

TO: Tina Levine/Dani Daniel, PM #4
Insecticide Branch/RD(7505C)

INTRODUCTION

The Bayer Corporation previously applied for registration of six new Advantage Plus insecticides [liquids containing 9.10% imidacloprid (Reg. No. 3125-414,98.0%) and 0.46% pyriproxyfen ([redacted] a.i.'s and 90.44% inerts] intended to kill fleas on different sizes of cats and dogs. The new products differs from the previous ones in that they include an insect growth regulator, pyriproxyfen, to help control flea eggs, and contains an additional inert. TRB

(L. Kutney) reviewed these data on June 2, 2000. All six products contain identical CSFs (dated 4-7-00) and separate proposed labels (dated 4-7-00). This review summarizes the Agency conclusions included in the June 2, 2000, review, Bayer's October 27, 2000, rebuttal to the Agency's conclusions and the Agency's response to Bayer's rebuttal.

Item 1

Agency Conclusion of June 2, 2000

Because the nominal concentrations of a.i.'s on the CSF are not identical to the label concentrations, the Registrant should resubmit the CSF and label and ensure that the concentrations of the a.i.'s are correct and identical.

Bayer's Rebuttal of October 27, 2000

"The nominal concentrations of a.i.'s on the CSFs and the draft product labels are identical. For example, the upper and lower certified limits for imidacloprid are 9.6% and 8.6%, respectively, and the nominal concentration for imadacloprid is 9.1% on both the CSF and the draft labeling. Please note, the upper, lower and nominal concentrations for imidacloprid are identical to those on the CSFs and labels for the 7 registered Advantage products (EPA Reg. Nos. 11556-116 through 11556-122). For ease of reference, a CSF for Advantage 10, EPA Reg. No. 11556-117, is enclosed. The Confidential Appendix of the review states *"The CSF for the subject product contains a nominal concentration of imidacloprid of 8.9% and of pyriproxyfen of 0.45% not 9.10% and 0.46%, respectively as stated on the proposed label."* As 8.9% is not on the CSF, we surmise that this value may have been calculated to correct for percent purity of the technical material. Thus, the nominal concentrations of the a.i.'s on the CSF are identical to the label concentrations, and the CSF and draft labeling for the Advantage Plus products are correct."

Agency Response of November 21

Subpart D-Product Chemistry Data Requirements, May 24, 2000, draft, defines the nominal concentration required by 158.155 as the "amount of active ingredient that is most likely to be present in the product when produced," in other words, the %active ingredient in the product (See also OPPTS 830.155, p.1). In addition, the nominal concentrations on the CSF and the draft label must be identical.

The Agency reiterates that *"The CSF for the subject product contains a nominal concentration of imidacloprid of 8.9% and of pyriproxyfen of 0.45% not 9.10% and 0.46%, respectively as stated on the proposed label."* Bayer is correct in assuming that the nominal concentration of imidacloprid is corrected to account for the fact that technical imidacloprid a.i. (Reg No. 3125-414) is 98.0% pure, and technical pyriproxyfen a.i. [redacted].
The nominal concentration of each a.i. from the CSF is calculated, as follows:

nominal concentration of the a.i. =

The amount of each a.i. (kg)., column 13a x (% purity of a.i. technical)
Total weight of components in column 13a

Bayer may either make sure that the label stated concentration is adjusted to be identical to the nominal concentrations of the a.i.'s or adjust the amount of each a.i. component so that the nominal concentration of each a.i. is identical to the proposed label concentration.

Item 2

Agency Conclusion of June 2, 2000

The name and address of the suppliers of inerts should be included on a revised CSF.

Bayer's Rebuttal of October 27, 2000

"Bayer acknowledges that the supplier(s) for "specialty" or proprietary materials must be listed on the CSF, but for those chemicals which are considered "commodity" chemicals, Bayer has not routinely listed the suppliers. As examples, the CSF's for the Advantage formulation (EPA Reg. Nos. 11556-116 through 11556-122) do not list the suppliers. The enclosed CSF for Advantage 10, EPA Reg. No. 11556-117, is a specific example. The Agency has permitted this in the past and acknowledges this practice which allows a change in source of these commodity chemicals without notification as permitted under PR Notice 98-10, Section III, B, 1.

As all of the inert ingredients in the proposed formulation for the A Plus products are commodity chemicals and are the same commodity chemicals which are in the Advantage formulation (Reg Nos 11556-116 through 11556-122) for which the Agency did not require the suppliers to be listed, Bayer would prefer not to list the suppliers of these chemicals for the Advantage Plus formulation."

Agency Response of November 21

The Agency routinely requests the names and addresses of suppliers of inerts on CSF's in order to be able to contact the supplier about the contents of their inerts, when necessary. The Instructions to EPA Form 8570-4, for Confidential Statement of Formula, Supplier Name and Address, number 11, specify that the Registrant should, "Provide the name and address of the supplier of each component in the (CSF) formulation. If one or more components will be obtained from more than one source, specify the names and addresses of the alternate sources also." There is no exception for "commodity chemicals."

A revised CSF including the name and address of the suppliers of inerts is still required.

Item 3

Agency Conclusion of June 2, 2000

The enforcement analytical method (40CFR 158.180) will be satisfactory, providing the Registrant submits a new copy not labeled "Confidential Business Information." This is a 3-97 FIFRA requirement (Section 10 (d)(1))needed for enforcement purposes, etc.

Bayer's Rebuttal of October 27; 2000

"One copy of the method without any "confidential" markings is included with this letter. Please note that this method is to be used for all six product applications.

Agency Response of November 21

An analytical method labeled "CBI" is not permitted as an enforcement method. The Agency acknowledges the receipt of the enforcement analytical method without this label and considers that the requirement for analytical method (40CFR 158.180) is now satisfied.

Item 4

Agency Conclusion of June 2, 2000

Group B Product chemistry requirements listed in Series 830 Guidelines under 40CFR 158.190 explodability (830-6315), Storage Stability of the Product (830-6317), miscibility (830-6319) and dielectric breakdown voltage (830-6321) have not been fulfilled and should be submitted.

Bayer's Rebuttal of October 27, 2000

Explodability "The OPPTS Test GDL 830.6316 for Explodability states 'The explodability test is necessary for use in precautionary labeling of pesticides when the product is potentially explosive.' Previous Agency guidance ('Roadmap for Guidance to Product Chemistry Guidelines' report from Anne Lindsay...) on this data requirement stated the requirement is for dusts and dusts from granular or powdered products. The Advantage Plus formulation is a liquid formulation. Moreover, it is not potentially explosive. The currently registered Advantage formulation is not potentially explosive and the Advantage Plus formulation would be even less explosive..."

Agency Response of November 21

Explodability

The Agency is aware that Advantage Plus is a liquid formulation. Section 158.190 of the 40 Code of Federal Regulations states that explodability testing is required if the product is

potentially explosive. However, the requirement for data concerning explodability definitely applies to liquid end use products as well as dusts and dusts from granular or powdered products. In fact, some liquids have a very high explosive potential, e.g., nitroglycerine.

Registrants are obliged to characterize the explodability of new end use products, in the absence of data or documentation to the contrary, the Agency may consider that any new product may be potentially explosive. Bayer has now certified that the currently registered Advantage formulation is not potentially explosive and the Advantage Plus formulation would be even less explosive...due to substitution of substitution of organic some organic solvent with water.

The requirement for explodability testing, OPPTS Test GDL 830.6316, is now satisfied.

Bayer's Rebuttal of October 27, 2000

Storage Stability As stated in 830.1000 Background for Product Properties Test Guidelines for the (viiii) OPPTS 830.6317 Storage Stability discussion on p 17:

- "The requirement for data (storage stability) on the EP applies on when: The product use pattern is one for which performance (efficacy) data are required (40CFR 158.640); the results of the storage stability study indicate that the concentration of any active ingredient is not within the certified limits or degradates of toxicological significance are detected in the study; or product instability is suspected or incidents of instability are reported."

Advantage Plus does not meet any of these conditions, as it is an EP, it is not registered for the use patterns for which efficacy data are required under 40 CFR 158.640, and the product/a. i.'s are known to be stable. Thus, storage stability data for the Advantage Plus formulation should not be required for submission.

Agency Response of November 21

Product Properties Test Guidelines OPPTS 830.6317 (b) for Storage Stability states that, "The objective of storage stability testing is to determine how long the product will retain the percent a.i. in its packaging material corresponding to its useful shelf life. The storage stability study provides data on change (or lack of change) in product composition over time, If certain ingredients decompose, other new chemicals are formed whose toxicity and other characteristics must be considered." Bayer should read 830.6317 for details concerning the requirements for storage stability testing. Storage stability testing is required end-use formulations, including the Advantage Plus formulation.

Bayer's Rebuttal of October 27, 2000

Miscibility GDL 830.6319 for Miscibility states:

- "This test is intended to determine whether a pesticide solution is suitable for application

after dilution with oil or other nonpolar solvents where applicable, instead of water. Data on miscibility also provide necessary information to support acceptable labeling for tank mix and spray applications (if the tank mix of the pesticide product is oil based or diluted with oil)."

Agency Response of November 21

GDL OPPTS 830.6319 for miscibility states, "Data on the physical and chemical characteristics of pesticide products are used to confirm or provide supportive information on their identity. Such data are used in reviewing the production or formulation process to produce the pesticide or product." However, the Agency is willing to concede that, as stated in 40 CFR 158.190 "the miscibility test is required if the liquid is an emulsifiable liquid and is to be diluted with petroleum solvents." Provided there is no alteration of use pattern for Advantage Plus which would involve dilution with petroleum or non-polar solvents, there will be no requirement imposed for miscibility testing.

Bayer's Rebuttal of October 27, 2000

Dielectric Breakdown Voltage

...Advantage Plus is to applied directly to dogs and cats in small volumes...use is not around electric equipment...

Agency Response of November 21

GDL 830.6321 states that dielectric breakdown voltage is required when the pesticide product is used on or in the vicinity of electrical equipment and electrical conduits. Dielectric breakdown voltage will not be required for this product, provided there is no alteration of use pattern which would increase exposure of the pesticide handlers to electrical equipment or electrical conduits.

The requirement for data concerning dielectric breakdown voltage is now satisfied.

SUBJECT: PRODUCT CHEMISTRY REVIEW OF MP [ ] EP [X]
DP BARCODE No.: D265763 REG./File Symbol No.: 11556-REA
PRODUCT NAME: Advantage Plus 9 for Cats
COMPANY: Bayer Corporation

1 Reviewer: Linda L. Kutney

2. Company: Bayer Corporation

3. Type of Submission: Registration [X] Reregistration [ ] New [X] Resubmission [ ] Amendment [ ] "ME-TOO" [X] Alternate Formulation [ ] Experimental Use Permit [ ] Other (Specify)

4. If "Me-TOO" Registration, this product is [ ] is not [X] similar or substantially similar to EPA's Reg. No.:
11556-116
If not, comment in Confidential Appendix on the significant differences between the registered and the new source.

CONFIDENTIAL STATEMENT OF FORMULA

5. Type of formulation and the sources of active ingredients:
- Non-integrated formulation system.....[X]
- Are all technical grade active ingredients used registered? ● yes [X] ● no [ ], If no, specify
- Integrated formulation system.....[ ]

6. Clearance of intentionally added ingredients in the formulation for the intended use (indicate in the Confidential Appendix those that are not cleared; the PC Codes should be provided by the chemist on the CSF for those that are cleared):

6(a) Formulation intended for food use under 40CFR§180.1001:
● yes [ ] ● no [X] ● Some are cleared, others are not [ ]
Cleared under list: ● c[ ] ● d[ ] ● e [ ]
Are there any limitations for use as an inert under 40CFR§180.1001?

● yes [ ] ● no [X], If yes, specify

6(b) Formulation intended for non-food use:
● yes [X] ● no [ ] ● Some are cleared, others are not [ ]

6(c) Clearance by the FDA of certain formulations under 21CFR§170 to 199,e.g.,(a) indirect food additives, such as food contact surface sanitizers; adhesives, coatings, paper and paperboard products that may contact food in packaging or holding; & (b) substances

generally recognized as safe,GRAS
● yes [ ] ● no [X] ● Some are cleared, others not [ ]
If yes, the entire formulation is cleared under 21CFR§

7. The density, pH, and flammability values given on the CSF are identical with those of GRN 830.7300(density), 830.7000(pH), and 830.6315(Flammability), respectively: ●
yes [X] ● no [ ]

8. The nominal concentrations (NC) of the active ingredients and the upper and lower certified limits (UCL & LCL) are as follows:

Active ingredient(s)	REG-NO	% by weight NC	UCL	LCL
Imidacloprid	3125-414	8.9	9.3	8.4
Pyriproxyfen	[redacted]	0.45	0.50	0.40

9. The calculated NCs, based on the pure active ingredients (PAI), are identical to those on the label:
● yes [ ] ● no [X]
Not acceptable for imidacloprid and Pyriproxyfen-as required in PR Notice 91-2

10. The certified limits are within the standard limits as per 40CFR§158.175 or are adequately explained if different: ● yes [ ] ● no [X]
PRODUCT LABEL

11. The chemical names of the active ingredients on the label are identical to those on the CSF: ● yes [X] ● no [ ]

12. The appropriate physical and chemical hazards statement regarding flammability or explosive characteristics of the product are given on the label:
● yes [ ] ● no [ ] ● not applicable [X]

13. The storage and disposal instructions for the pesticide and container are in compliance with PR Notice 84-1 for household use products or PR Notice 83-3 for all other uses:
● yes [X] ● no [ ]

PRODUCT CHEMISTRY DATA (SERIES 830 Subgroup A & Subgroup B)

14. Chemical IDs/Manufacture/ Analytical Information New Guideline:830.--	Data Required Fulfilled	MRID No.
1550. Chemical Identity(CSF)	N	450969-02
1600. Beginning Materials 1620. Formulation Process	Y	450969-02
1670. Discussion of Impurities	Y	450969-02
1700. Preliminary Analysis	Y	450969-02
1750. Certified Limits(CSF)	N	450969-02
1800. Enforcement of Analytical Method	Y	450969-01

15. Physical/Chemical Properties New Guideline No. 830.---	Data Required Fulfilled	Value or Qualitat. Descrip.	MRID No.
6303. Physical State	Y	Liquid	450969-03
7300. Density/Bulk Density	Y	1.092 lbs/gal	450969-03
7000. pH	NA	6.02	450969-03
6314. Oxid/Red Action	Y	No ox. Or red.. Action	450969-03
6315. Flammability-Flash Point	Y	above 100.2°C	450969-03
6315. Flame Extension	NA		--
6316. Explodability	Y	--	10-27-00 Bayer rebuttal
6317. Storage Stability.	N	--	--
7100. Viscosity	Y	5.13 cSt	450969-03

6319. Miscibility	Y	--	10-27-00 Bayer rebuttal
6320. Corrosion Characteristics	Y	Non-corrosive as packaged, tested for about 30 days	450969-03
6321. Dielectric Breakdown Voltage	Y	---	10-27-00 Bayer rebuttal

Explanations: Y = The Requirements Were Fulfilled; N = The Requirements Were Not Fulfilled; NA = Not Applicable; G = Data Gap; U = Requires Upgrading; I = Incomplete or In Progress; W = Waived.

DATE: 22/NOV/2000

SUBJECT: PRODUCT CHEMISTRY REVIEW OF MP [ ] EP's [X]

DP BARCODE No.: D270181
REG./File Symbol No.: 11556-REA
PRODUCT NAME: Advantage Plus 9 for Cats
AND
DP BARCODE No.: D270183
REG./File Symbol No.: 11556-REI
PRODUCT NAME: Advantage Plus 10 for Dogs
AND
DP BARCODE No.: D270184
REG./File Symbol No.: 11556-REL
PRODUCT NAME: Advantage Plus 20 for Dogs
AND
DP BARCODE No.: D270182
REG./File Symbol No.: 11556-REO
PRODUCT NAME: Advantage Plus 18 for Cats
AND
DP BARCODE No.: D270186
REG./File Symbol No.: 11556-RET
PRODUCT NAME: Advantage Plus 55 for Dogs
AND
DP BARCODE No.: D270188
REG./File Symbol No.: 11556-RGN
PRODUCT NAME: Advantage Plus 100 for Dogs

COMPANY: Bayer Corporation

FROM: Linda L. Kutney, Chemist
Product Chemistry Team
Technical Review Branch (TRB)/RD (7505C)

TO: Tina Levine/Dani Daniel, PM #4
Insecticide Branch/RD(7505C)

INTRODUCTION

The Bayer Corporation previously applied for registration of six new Advantage Plus insecticides [liquids containing 9.10% imidacloprid (Reg. No. 3125-414,98.0%) and 0.46% pyriproxyfen ([redacted] a.i.'s and 90.44% inerts] intended to kill fleas on different sizes of cats and dogs. The new products differs from the previous ones in that they include an insect growth regulator, pyriproxyfen, to help control flea eggs, and contains an additional inert. TRB

(L. Kutney) reviewed these data on June 2, 2000. All six products contain identical CSFs (dated 4-7-00) and separate proposed labels (dated 4-7-00). This review summarizes the Agency conclusions included in the June 2, 2000, review, Bayer's October 27, 2000, rebuttal to the Agency's conclusions and the Agency's response to Bayer's rebuttal.

Item 1

Agency Conclusion of June 2, 2000

Because the nominal concentrations of a.i.'s on the CSF are not identical to the label concentrations, the Registrant should resubmit the CSF and label and ensure that the concentrations of the a.i.'s are correct and identical.

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"The nominal concentrations of a.i.'s on the CSFs and the draft product labels are identical. For example, the upper and lower certified limits for imidacloprid are 9.6% and 8.6%, respectively, and the nominal concentration for imadacloprid is 9.1% on both the CSF and the draft labeling. Please note, the upper, lower and nominal concentrations for imidacloprid are identical to those on the CSFs and labels for the 7 registered Advantage products (EPA Reg. Nos. 11556-116 through 11556-122). For ease of reference, a CSF for Advantage 10, EPA Reg. No. 11556-117, is enclosed. The Confidential Appendix of the review states *"The CSF for the subject product contains a nominal concentration of imidacloprid of 8.9% and of pyriproxyfen of 0.45% not 9.10% and 0.46%, respectively as stated on the proposed label."* As 8.9% is not on the CSF, we surmise that this value may have been calculated to correct for percent purity of the technical material. Thus, the nominal concentrations of the a.i.'s on the CSF are identical to the label concentrations, and the CSF and draft labeling for the Advantage Plus products are correct."

Agency Response of November 21

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The Agency reiterates that *"The CSF for the subject product contains a nominal concentration of imidacloprid of 8.9% and of pyriproxyfen of 0.45% not 9.10% and 0.46%, respectively as stated on the proposed label."* Bayer is correct in assuming that the nominal concentration of imidacloprid is corrected to account for the fact that technical imidacloprid a.i. (Reg No. 3125-414) is 98.0% pure, and technical pyriproxyfen a.i. [redacted].
The nominal concentration of each a.i. from the CSF is calculated, as follows:

nominal concentration of the a.i. =

The amount of each a.i. (kg)., column 13a x (% purity of a.i. technical)
Total weight of components in column 13a

Bayer may either make sure that the label stated concentration is adjusted to be identical to the nominal concentrations of the a.i.'s or adjust the amount of each a.i. component so that the nominal concentration of each a.i. is identical to the proposed label concentration.

Item 2

Agency Conclusion of June 2, 2000

The name and address of the suppliers of inerts should be included on a revised CSF.

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A revised CSF including the name and address of the suppliers of inerts is still required.

Item 3

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"One copy of the method without any "confidential" markings is included with this letter. Please note that this method is to be used for all six product applications.

Agency Response of November 21

An analytical method labeled "CBI" is not permitted as an enforcement method. The Agency acknowledges the receipt of the enforcement analytical method without this label and considers that the requirement for analytical method (40CFR 158.180) is now satisfied.

Item 4

Agency Conclusion of June 2, 2000

Group B Product chemistry requirements listed in Series 830 Guidelines under 40CFR 158.190 explodability (830-6315), Storage Stability of the Product (830-6317), miscibility (830-6319) and dielectric breakdown voltage (830-6321) have not been fulfilled and should be submitted.

Bayer's Rebuttal of October 27, 2000

Explodability "The OPPTS Test GDL 830.6316 for Explodability states 'The explodability test is necessary for use in precautionary labeling of pesticides when the product is potentially explosive.' Previous Agency guidance ('Roadmap for Guidance to Product Chemistry Guidelines' report from Anne Lindsay...) on this data requirement stated the requirement is for dusts and dusts from granular or powdered products. The Advantage Plus formulation is a liquid formulation. Moreover, it is not potentially explosive. The currently registered Advantage formulation is not potentially explosive and the Advantage Plus formulation would be even less explosive..."

Agency Response of November 21

Explodability

The Agency is aware that Advantage Plus is a liquid formulation. Section 158.190 of the 40 Code of Federal Regulations states that explodability testing is required if the product is

potentially explosive. However, the requirement for data concerning explodability definitely applies to liquid end use products as well as dusts and dusts from granular or powdered products. In fact, some liquids have a very high explosive potential, e.g., nitroglycerine.

Registrants are obliged to characterize the explodability of new end use products, in the absence of data or documentation to the contrary, the Agency may consider that any new product may be potentially explosive. Bayer has now certified that the currently registered Advantage formulation is not potentially explosive and the Advantage Plus formulation would be even less explosive...due to substitution of substitution of organic some organic solvent with water.

The requirement for explodability testing, OPPTS Test GDL 830.6316, is now satisfied.

Bayer's Rebuttal of October 27, 2000

Storage Stability As stated in 830.1000 Background for Product Properties Test Guidelines for the (viiii) OPPTS 830.6317 Storage Stability discussion on p 17:

- "The requirement for data (storage stability) on the EP applies on when: The product use pattern is one for which performance (efficacy) data are required (40CFR 158.640); the results of the storage stability study indicate that the concentration of any active ingredient is not within the certified limits or degradates of toxicological significance are detected in the study; or product instability is suspected or incidents of instability are reported."

Advantage Plus does not meet any of these conditions, as it is an EP, it is not registered for the use patterns for which efficacy data are required under 40 CFR 158.640, and the product/a. i.'s are known to be stable. Thus, storage stability data for the Advantage Plus formulation should not be required for submission.

Agency Response of November 21

Product Properties Test Guidelines OPPTS 830.6317 (b) for Storage Stability states that, "The objective of storage stability testing is to determine how long the product will retain the percent a.i. in its packaging material corresponding to its useful shelf life. The storage stability study provides data on change (or lack of change) in product composition over time, If certain ingredients decompose, other new chemicals are formed whose toxicity and other characteristics must be considered." Bayer should read 830.6317 for details concerning the requirements for storage stability testing. Storage stability testing is required end-use formulations, including the Advantage Plus formulation.

Bayer's Rebuttal of October 27, 2000

Miscibility GDL 830.6319 for Miscibility states:

- "This test is intended to determine whether a pesticide solution is suitable for application

after dilution with oil or other nonpolar solvents where applicable, instead of water. Data on miscibility also provide necessary information to support acceptable labeling for tank mix and spray applications (if the tank mix of the pesticide product is oil based or diluted with oil)."

Agency Response of November 21

GDL OPPTS 830.6319 for miscibility states, "Data on the physical and chemical characteristics of pesticide products are used to confirm or provide supportive information on their identity. Such data are used in reviewing the production or formulation process to produce the pesticide or product." However, the Agency is willing to concede that, as stated in 40 CFR 158.190 "the miscibility test is required if the liquid is an emulsifiable liquid and is to be diluted with petroleum solvents." Provided there is no alteration of use pattern for Advantage Plus which would involve dilution with petroleum or non-polar solvents, there will be no requirement imposed for miscibility testing.

Bayer's Rebuttal of October 27, 2000

Dielectric Breakdown Voltage

...Advantage Plus is to applied directly to dogs and cats in small volumes...use is not around electric equipment...

Agency Response of November 21

GDL 830.6321 states that dielectric breakdown voltage is required when the pesticide product is used on or in the vicinity of electrical equipment and electrical conduits. Dielectric breakdown voltage will not be required for this product, provided there is no alteration of use pattern which would increase exposure of the pesticide handlers to electrical equipment or electrical conduits.

The requirement for data concerning dielectric breakdown voltage is now satisfied.

SUBJECT: PRODUCT CHEMISTRY REVIEW OF MP [ ] EP [X]
DP BARCODE No.: D265763 REG./File Symbol No.: 11556-REA
PRODUCT NAME: Advantage Plus 9 for Cats
COMPANY: Bayer Corporation

1 Reviewer: Linda L. Kutney

2. Company: Bayer Corporation

3. Type of Submission: Registration [X] Reregistration [ ] New [X] Resubmission [ ] Amendment [ ] "ME-TOO" [X] Alternate Formulation [ ] Experimental Use Permit [ ] Other (Specify)

4. If "Me-TOO" Registration, this product is [ ] is not [X] similar or substantially similar to EPA's Reg. No.:
11556-116
If not, comment in Confidential Appendix on the significant differences between the registered and the new source.

CONFIDENTIAL STATEMENT OF FORMULA

5. Type of formulation and the sources of active ingredients:
- Non-integrated formulation system.....[X]
- Are all technical grade active ingredients used registered? ● yes [X] ● no [ ], If no, specify
- Integrated formulation system.....[ ]

6. Clearance of intentionally added ingredients in the formulation for the intended use (indicate in the Confidential Appendix those that are not cleared; the PC Codes should be provided by the chemist on the CSF for those that are cleared):

6(a) Formulation intended for food use under 40CFR§180.1001:
● yes [ ] ● no [X] ● Some are cleared, others are not [ ]
Cleared under list: ● c[ ] ● d[ ] ● e [ ]
Are there any limitations for use as an inert under 40CFR§180.1001?

● yes [ ] ● no [X], If yes, specify

6(b) Formulation intended for non-food use:
● yes [X] ● no [ ] ● Some are cleared, others are not [ ]

6(c) Clearance by the FDA of certain formulations under 21CFR§170 to 199,e.g.,(a) indirect food additives, such as food contact surface sanitizers; adhesives, coatings, paper and paperboard products that may contact food in packaging or holding; & (b) substances

generally recognized as safe,GRAS
● yes [ ] ● no [X] ● Some are cleared, others not [ ]
If yes, the entire formulation is cleared under 21CFR§

7. The density, pH, and flammability values given on the CSF are identical with those of GRN 830.7300(density), 830.7000(pH), and 830.6315(Flammability), respectively: ●
yes [X] ● no [ ]

8. The nominal concentrations (NC) of the active ingredients and the upper and lower certified limits (UCL & LCL) are as follows:

Active ingredient(s)	REG-NO	% by weight NC	UCL	LCL
Imidacloprid	3125-414	8.9	9.3	8.4
Pyriproxyfen	[redacted]	0.45	0.50	0.40

9. The calculated NCs, based on the pure active ingredients (PAI), are identical to those on the label:
● yes [ ] ● no [X]
Not acceptable for imidacloprid and Pyriproxyfen-as required in PR Notice 91-2

10. The certified limits are within the standard limits as per 40CFR§158.175 or are adequately explained if different: ● yes [ ] ● no [X]
PRODUCT LABEL

11. The chemical names of the active ingredients on the label are identical to those on the CSF: ● yes [X] ● no [ ]

12. The appropriate physical and chemical hazards statement regarding flammability or explosive characteristics of the product are given on the label:
● yes [ ] ● no [ ] ● not applicable [X]

13. The storage and disposal instructions for the pesticide and container are in compliance with PR Notice 84-1 for household use products or PR Notice 83-3 for all other uses:
● yes [X] ● no [ ]

PRODUCT CHEMISTRY DATA (SERIES 830 Subgroup A & Subgroup B)

14. Chemical IDs/Manufacture/ Analytical Information New Guideline:830.--	Data Required Fulfilled	MRID No.
1550. Chemical Identity(CSF)	N	450969-02
1600. Beginning Materials 1620. Formulation Process	Y	450969-02
1670. Discussion of Impurities	Y	450969-02
1700. Preliminary Analysis	Y	450969-02
1750. Certified Limits(CSF)	N	450969-02
1800. Enforcement of Analytical Method	Y	450969-01

15. Physical/Chemical Properties New Guideline No. 830.---	Data Required Fulfilled	Value or Qualitat. Descrip.	MRID No.
6303. Physical State	Y	Liquid	450969-03
7300. Density/Bulk Density	Y	1.092 lbs/gal	450969-03
7000. pH	NA	6.02	450969-03
6314. Oxid/Red Action	Y	No ox. Or red. Action	450969-03
6315. Flammability-Flash Point	Y	above 100.2°C	450969-03
6315. Flame Extension	NA		--
6316. Explodability	Y	--	10-27-00 Bayer rebuttal
6317. Storage Stability.	N	--	--
7100. Viscosity	Y	5.13 cSt	450969-03

6319. Miscibility	Y	--	10-27-00 Bayer rebuttal
6320. Corrosion Characteristics	Y	Non-corrosive as packaged, tested for about 30 days	450969-03
6321. Dielectric Breakdown Voltage	Y	---	10-27-00 Bayer rebuttal

Explanations: Y = The Requirements Were Fulfilled; N = The Requirements Were Not Fulfilled; NA = Not Applicable; G = Data Gap; U = Requires Upgrading; I = Incomplete or In Progress; W = Waived.

Bayer

Agriculture Division

Animal Health

Bayer Corporation
P.O. Box 390
Shawnee Mission, KS 66201-0390
Phone: 913 268-2000

via Federal Express

October 27, 2000

Ms. Dani Daniel
Registration Division (H7505C)
U.S. Environmental Protection Agency
Ariel Rios Building
1200 Pennsylvania Avenue, NW
Washington, DC 20460

Subject: Response to Product Chemistry Review for Advantage® Plus 9, 18, 10, 20, 55, and 100 Products (EPA File Symbols 11556-REO, -REA, -REI, -REL, -RET, -RGN)

Dear Ms. Daniel:

Bayer Corporation received product chemistry reviews (dated June 16, 2000) from the Agency on June 22, 2000 for the six products referenced above. The reviews stated that product labels and confidential statements of formula (CSFs) contain a number of deficiencies that need to be addressed. In addition, you requested that we should make no label changes until the entire package (domestic animal safety and acute toxicity) has been reviewed. The following is Bayer's response to the Agency's product chemistry reviews. Please note that the same deficiencies were identified by the reviewer for all six products as the formulation and nominal label concentrations are the same for all six produets.

The deficiencies and Bayer's responses are detailed below:

Item 1

Agency conclusion: *"Because the nominal concentrations of a.i.'s on the CSF are not identical to the label concentrations, the Registrant should resubmit the CSF and label and ensure that the concentrations of the a.i.'s are correct and identical."*

Bayer response: The nominal concentrations of a.i.'s on the CSFs and the draft product product labels are identical. For example, the upper and lower certified limits for imidacloprid are 9.6% and 8.6%, respectively, and the nominal concentration for imidacloprid is 9.1% on both the CSF and the draft labeling. Please note, the upper, lower and nominal concentrations for imidacloprid are identical to those on the CSF's and labels for the 7 currently registered Advantage products (EPA Reg. Nos. 11556-116

through 11556-122). For ease of reference, a CSF for Advantage 10, EPA Reg. No. 11556-117, is enclosed. The Confidential Appendix of the review states *"The CSF for the subject product contains a nominal concentration of imidacloprid of 8.9% and of pyriproxyfen of 0.45%, not 9.10% and 0.46%, respectively as stated on the proposed label."* As 8.9% is not on the CSF, we surmise that this value may have been calculated to correct the CSF values for the percent purity of the active ingredients. However, the active ingredient values listed on the CSF have already been corrected for percent purity of the technical material. Thus, the nominal concentrations of the a.i.'s on the CSF are identical to the label concentrations, and the CSF and draft labeling for the Advantage Plus products are correct.

Item 2 Agency conclusion: *"The name and address of the suppliers of inerts should be included on a revised CSF."*

Bayer response: Bayer acknowledges that the supplier(s) for "specialty" or "proprietary" materials must be listed on the CSF, but for those chemicals which are considered "commodity" chemicals, Bayer has not routinely listed the suppliers. As examples, the CSF's for the Advantage formulation (EPA Reg. Nos. 11556-116 through 11556-122) do not list the suppliers. The enclosed CSF for Advantage 10, EPA Reg. No. 11556-117 is a specific example. The Agency has permitted this in the past and acknowledges this practice which allows a change in a source of these commodity chemicals without notification as permitted under PR Notice 98-10, Section III, B, 1.

As all of the inert ingredients in the proposed formulation for the Advantage Plus products (EPA File Symbols 11556-REO, -REA, -REI, -REL, -RET, and -RGN) are commodity chemicals and are the same commodity chemicals which are in the Advantage formulation (EPA Reg. Nos. 11556-116 through 11556-122) for which the Agency did not require the suppliers to be listed, Bayer would prefer not to list the suppliers of these chemicals for the Advantage Plus formulation.

Item 3 Agency conclusion: *"The enforcement analytical method (40CFR 158.180) will be satisfactory, providing the Registrant submits a new copy not labeled 'Confidential Business Information.' This is a 3-97 FIFRA requirement (Section 10 (d)(1)) needed for enforcement purposes, etc."*

Bayer response: One copy of the method without any "confidential" markings is included with this letter. Please note that this method is to be used for all six product applications.

Item 4 Agency conclusion: *"Group B product chemistry requirements listed in Series 830 Guidelines under 40CFR 158.190 explodability (830-6315), storage stability of the product (830-6317), miscibility (830-6319) and dielectric breakdown voltage (830-6321) have not been fulfilled and should be submitted."*

Bayer response: These tests are not required under 40CFR 158.190 or PR Notice 92-5. Each item is discussed in detail below.

Explodability. The OPPTS Test Guideline 830.6316 for Explodability states, "The explodability test is necessary for use in precautionary labeling of pesticides when the product is potentially explosive." Previous Agency guidance ("Roadmap for Guidance to Product Chemistry Guidelines" report from Anne E. Lindsay, Director of the Registration Division, to Margaret Stasikowski, Deputy Director of Special Review and Reregistration Division) on this data requirement stated the requirement is for dusts and dusts from granular or powdered products. The Advantage Plus formulation is a liquid formulation. Moreover, it is not potentially explosive. The currently registered Advantage formulation is not potentially explosive, and the Advantage Plus formulation would be even less explosive as the formulation is very similar to the Advantage formulation in that some of the organic solvent has been removed and substituted with water and 0.46% pyriproxyfen which is not explosive.

Storage Stability. As stated in the OPPTS 830.1000 Background for Product Properties Test Guidelines for the (viii) OPPTS 830.6317 Storage Stability discussion on page 17:

> "The requirement for data (storage stability) on the EP applies on when: The product use pattern is one for which performance (efficacy) data are required (40 CFR 158.640); the results of the storage stability study indicate that the concentration of any active ingredient is not within the certified limits or degradates of toxicological significance are detected in the study; or product instability is suspected or incidents of instability are reported."

Advantage Plus does not meet any of these conditions, as it is an EP (end-use product), it is not registered for the use patterns for which efficacy data are required under 40 CFR 158.640, and the product/active ingredients are known to be stable. Thus, storage stability data for the Advantage Plus formulation should not be required for submission.

Miscibility. The OPPTS Test Guideline 830.6319 for Miscibility states:

> "This test is intended to determine whether a pesticide solution is suitable for application after dilution with oil or other nonpolar solvents, where applicable, instead of water. Data on miscibility also provide necessary information to support acceptable labeling for tank mix and spray applications (if the tank mix of the pesticide product is oil, based or diluted with oil)."

The Advantage Plus formulation is a ready-to-use liquid for direct application in small amounts (no greater than 4.0 ml) directly to dogs or cats. The Advantage Plus formulation is not to be diluted with any material and obviously is not intended for tank mix and spray applications. Thus, miscibility data are not applicable and should not be required for the Advantage Plus formulation.

Dielectric Breakdown Voltage. The OPPTS Test Guideline 830.6321 for Dielectric Breakdown Voltage states the following:

> "The objective of this test is to determine the potential for hazard when the pesticide product is used on or in the vicinity of electrical equipment and electrical conduits. The dielectric breakdown voltage of an insulating liquid is of importance as a measure of the liquid's ability to withstand electric stress without failure. Data is required when the end-use product is a nonconductant liquid and is to be used around electrical equipment."

The Advantage Plus formulation is to be applied directly to dogs and cats in small volumes (again, never more than 4.0 ml even with the largest animals). Clearly this use is not around electric equipment, and thus, these data are not applicable and should not be required for the Advantage Plus formulation.

With the enclosed enforcement method and rationale for not needing testing for explodability, storage stability, dielectric breakdown voltage and miscibility, all the Agency's requirements for product chemistry for the Advantage® Plus products (EPA File Symbols 11556-REO, -REA, -REI, -REL, -RET, -RGN) should be fulfilled.

Please call me at (913) 268-2751 if you have any questions or need additional information.

Sincerely,

Gregory G. Gagliano
Manager, Environmental Research

GGG/lt

Enclosures

Pages 47-52 - *Access to FIFRA health and safety data is restricted under FIFRA

Page 53 Confidential Statement of Formula may be entitled to confidential treatment

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

OCT 5 2000

Mr. F. Terry McNamara
Bayer Corporation
Animal Health, Agriculture Division
P.O. Box 390
Shawnee Mission, KS 66201

Subject: Applications for New Advantage Products
Reg. No. 11556-REA, REO, REI, REL, RET, RGN
Your submission date, April 7, 2000

Dear Mr. McNamara:

Enclosed are the final two animal safety study reviews, for registration numbers 11556-REA and REO. You should now have complete package. If you are missing any reviews, please let me know.

The labeling referred to above, submitted in connection with the above registrations under the Federal Insecticide, Fungicide, and Rodenticide Act is not acceptable for the reasons below:

As indicated in my June 16, 2000, letter a number of deficiencies exist with your labels and confidential statements of formula that need to be corrected before a registration can be given. The following are deficiencies are can be found in the product chemistry review:

1. The proposed labels should contain a "Note to Physician". The following statements are suggested types of information that may be included, if applicable:

-technical information on symptomatology;
-use of supportive treatments to maintain life functions;
-medicine that will counteract the specific physiological effects of the pesticide;
-company telephone number to specific medical personnel who can provide specialized medical advice.

2. Because the nominal concentrations of a.i.'s on the CSF are not identical to the label concentrations, the Registrant should resubmit the CSF and label and ensure that the

concentrations of the a.i.'s are correct and identical.

3. The name and address of the suppliers of inserts should be included on a revised CSF.

4. The enforcement analytical method will be satisfactory, providing the Registrant submits a new copy not labeled "confidential Business Information." This is a 3-97 FIFRA requirement (Section 10(d)(1) needed for enforcement purposes, etc.

5. Group B product chemistry requirements listed in series 830 guidelines under 40CFR 158.190 explodability (830-6315), Storage Stability of the product (830-6317), miscibility (830-6319) and dielectric breakdown voltage (830-6321) have not been fulfilled and should be submitted.

6. None of the subject products are substantially similar to any of the parent products from a product chemistry point of view, because they each contain an additional a.i. and inert ingredient, and because the nominals and certified limits of the components are not substantially similar.

Please read the reviews and make changes as specified. Upon making the changes, please resubmit your labels and CSFs. If there are question, call me at 703 305-5409.

Sincerely,

/s/

Dani Daniel
Insecticide-Rodenticide Branch
Registration Division 7505C

Enclosure:

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF PREVENTION,
PESTICIDES AND TOXIC SUBSTANCES

22/SEP/2000

MEMORANDUM

Subject: EPA File Symbol: 11556-REA Advantage Plus 9 for Cat,
11556-REO Advantage Plus 18 for Cats
DP Barcodes: D265762 and D265765
Case No: 068807, 068810
PC Code: 129099

From: Masih Hashim, Toxicologist MH
Technical Review Branch JCR
Registration Division (7505C)

To: Helene Daniel/Tina Levine, PM 04
Insecticide Rodenticide Branch
Registration Division (7505C)

Registrant: Bayer Corporation

ACTION REQUESTED: The Registrant requests a review of the companion animal safety study (MRID 45097001), Advantage Plus® 9 and 18 for cats with: 9.1% Imidacloprid w/w; 0.9% Pyriproyfen w/w (active ingredients). The compound was topically applied at 5 times (limit test) the recommended dose to groups of 6 male and 6 female cats. Animals were treated on study days 0, 7, 14, and 21.

COMMENTS/RECOMMENDATIONS:

The study MRID 45097001 was conducted at 5X the specified application rate; which demonstrates an adequate safety margin for adult cats. There was no repeated toxicological response in cats following exposure to the proposed formulation. Any such response is random and is seen in the earlier phase of study. This cat study has been classified as **Acceptable.**

The Products: 11556-REA and/or 11556-REO have Imidacloprid 9.15% and Pyriproxyfen 0.9%. However, the label states 9.1% Imidacloprid and 0.46% pyriproxyfen, having same formulation for both products.

This product has residential uses and an Oral LD_{50} value < 1500 mg/kg, which would require the Child Resistant Packaging.

Acute toxicology profile for the Product is as follows:

Acute Oral LD_{50}	III	acceptable
Acute Dermal LD_{50}	IV	acceptable
Acute Inhalation LC_{50}	IV	acceptable
Primary Eye Irritation	III	acceptable
Primary Dermal Irritation	IV	acceptable
Dermal Sensitization	neg	acceptable

Primary review of the Companion Animal Safety Study was conducted by an Agency Contractor, then revised by the Technical Review Branch. There are two labels, one for Advantage Plus 9 for Cats and the other for Advantage Plus 18 for Cats.

Following is the Executive Summary of the study:

In a companion animal safety study (MRID 45097001), Advantage Plus® 9 and 18 for cats (Active Ingredients: 9.1% Imidacloprid w/w; 0.9% Pyriproyfen w/w) was topically applied at dose volumes of 2.0 ml for cats weighing less than or equal to 9 lbs, and 4.0 mL for cats weighing greater than 9 lbs (5 times the recommended doses) to groups of 6 male and 6 female cats, 7 months to one year of age. Controls were dosed with the vehicle at volumes of 2.0 mL for cats weighing less than or equal to 9 lbs and 4.0 ml for cats weighing greater than 9 lbs (5.6 times the volume of vehicle in the recommended doses). Animals were treated on (study) days 0, 7, 14, and 21.

Treatment related clinical signs included transient salivation which ceased within 2 hours of treatment on day 0 (4 of 12 test animals and 1 of 12 vehicle control animals reported from licking the test material), and a rough hair coat appearance at the treatment site on all animals of both groups following treatment on days 14 and 21. None of the cats were observed salivating following the last 3 treatments. One animal from the test group had pruritis at one hour on day 21. There was vomiting by two cats in the test group on days 19 and 25, which did not occur in periods following the test (substance) applications. Vomiting may be associated with licking the test substance. This does not appear to be exposure related. There were loose stools from two cats in the control group. Additionally, one male from the control group exhibited inappetence on days 22-24 and was observed to be circling and unsteady at the p.m. observation period on day 23. The clinical chemistry and hematology findings from this cat on day 22 were consistent with hemoconcentration due to dehydration. Possible cause of these signs was not clear. His behavior and appetite were normal for the remainder of the study, as were his clinical pathology parameters. There were no other treatment related effects on hematology, coagulation or clinical chemistry parameters. There were no treatment related effects on body weight or food consumption, and there were no signs of irritation at the application sites.

Currently there is a product in the market with 9.1% Imidacloprid. The proposed product is adding 0.46% Pyriproxyfen to the current product. The added ingredient has low acute and chronic toxicity in mammalian species.

Any clinical signs on the study showed no consistent toxicological response. This study is classified as **Acceptable /Guideline** for a companion animal safety study (OPPTS 870.7200) in cats .

LABELING:

Date: 09/28/00 LABEL REVIEW SYSTEM

ID #: 011556-00126 Advantage Plus 9 for Cats

SIGNAL WORD: CAUTION

PRECAUTIONARY STATEMENTS:

Harmful if swallowed. Causes moderate eye irritation. Avoid contact with eyes or clothing.

STATEMENT OF PRACTICAL TREATMENT (SOPT):

IF SWALLOWED: Call a poison control center or doctor immediately for treatment advice. Have person sip a glass of water if able to swallow. Do not induce vomiting unless told to by a poison control center or doctor. Do not give anything by mouth to an unconscious person.

IF IN EYES: Hold eye open and rinse slowly and gently with water for 15-20 minutes. Remove contact lenses, if present, after the first 5 minutes, then continue rinsing eye. Call a poison control center or doctor for treatment advice.

NOTE TO PHYSICIAN:

Note to PM/CRM/Registrant: The proposed label should contain a "Note to Physician." The following statements are suggested types of information that may be included, if applicable:

- technical information on symptomatology;
- use of supportive treatments to maintain life functions;
- medicine that will counteract the specific physiological effects of the pesticide;
- company telephone number to specific medical personnel who can provide specialized medical advice.

USER SAFETY RECOMMENDATION

Wash hands before eating, drinking, chewing gum, using tobacco or using the toilet.

ID #: 011556-00129 Advantage Plus 18 for Cats

SIGNAL WORD: CAUTION

PRECAUTIONARY STATEMENTS:

Harmful if swallowed. Causes moderate eye irritation. Avoid contact with eyes or clothing.

STATEMENT OF PRACTICAL TREATMENT (SOPT):

IF SWALLOWED: Call a poison control center or doctor immediately for treatment advice. Have person sip a glass of water if able to swallow. Do not induce vomiting unless told to by a poison control center or doctor. Do not give anything by mouth to an unconscious person.

IF IN EYES: Hold eye open and rinse slowly and gently with water for 15-20 minutes. Remove contact lenses, if present, after the first 5 minutes, then continue rinsing eye. Call a poison control center or doctor for treatment advice.

NOTE TO PHYSICIAN:

Note to PM/CRM/Registrant: The proposed label should contain a "Note to Physician." The following statements are suggested types of information that may be included, if applicable:

- technical information on symptomatology;
- use of supportive treatments to maintain life functions;
- medicine that will counteract the specific physiological effects of the pesticide;
- company telephone number to specific medical personnel who can provide specialized medical advice.

USER SAFETY RECOMMENDATIONS: Wash hands before eating, drinking, chewing gum, using tobacco or using the toilet.

DATA EVALUATION REPORT

ADVANTAGE PLUS® 9 AND 18 FOR CATS
[9.1% Imidacloprid with 0.9% Pyriproxyfen Spot-on Formulation]

STUDY TYPE: Companion Animal Safety - Cat (OPPTS 870.7200)
MRID 45097001

Prepared for

Registration Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

Chemical Hazard Evaluation Group
Toxicology and Risk Analysis Section
Life Sciences Division
Oak Ridge National Laboratory
Oak Ridge, TN 37831

Primary Reviewer: Donna L. Fefee, D.V.M..	Signature: Date:	Robert H. Ross for D.L. Fefee AUG 14 2000
Secondary Reviewers: Cheryl B. Bast, Ph.D., D.A.B.T.	Signature: Date:	Cheryl B Bast AUG 14 2000
Robert H. Ross, M.S., Group Leader	Signature: Date:	Robert H. Ross AUG 14 2000
Quality Assurance: Lee Ann Wilson, M.A.	Signature: Date:	L. A. Wilson AUG 14 2000

Disclaimer

This review may have been altered subsequent to the contractors signatures above.

Oak Ridge National Laboratory, Managed and Operated by UT-Battelle, LLC, for the U.S. Department of Energy under contract number DE-AC05-00OR22725.

DATA EVALUATION RECORD

STUDY TYPE: Companion Animal Safety/Cats[OPPTS 870.7200]

EPA I.D. NUMBERS: DP BARCODES: D265762, D265765; MRID NUMBER: 45097001

TEST MATERIAL: Advantage Plus® 9 and 18 for Cats

STUDY NUMBER: 75122 (150.853)

TESTING FACILITY: Bayer Corporation, Agriculture Division, Animal Health, DeSoto Research Facility, 35040 West 87th Street, Building Number 20, DeSoto, Kansas 66018.

SPONSOR: Bayer Corporation, Agriculture Division, Animal Health

TITLE OF REPORT: Evaluation of the general safety of 9.1% Imidacloprid with 0.9% pyriproxyfen spot-on formulation in the target species, adult cats.

AUTHOR: A.S. Abraham

REPORT ISSUED: April 4, 2000

EXECUTIVE SUMMARY:.

In a companion animal safety study (MRID 45097001), Advantage Plus® 9 and 18 for cats (Active Ingredients: 9.1% Imidacloprid w/w; 0.9% Pyriproyfen w/w) was topically applied at dose volumes of 2.0 ml for cats weighing less than or equal to 9 lbs, and 4.0 mL for cats weighing greater than 9 lbs (5 times the recommended doses) to groups of 6 male and 6 female cats, 7 months to one year of age. Controls were dosed with the vehicle at volumes of 2.0 mL for cats weighing less than or equal to 9 lbs and 4.0 ml for cats weighing greater than 9 lbs (5.6 times the volume of vehicle in the recommended doses). Animals were treated on (study) days 0, 7, 14, and 21.

Treatment related clinical signs included transient salivation which ceased within 2 hours of treatment on day 0 (4 of 12 test animals and 1 of 12 vehicle control animals reported from licking the test material), and a rough hair coat appearance at the treatment site on all animals of both groups following treatment on days 14 and 21. None of the cats were observed salivating following the last 3 treatments. One animal from the test group had pruritis at one hour on day 21. There was vomiting by two cats in the test group on days 19 and 25, which did not occur in periods following the test (substance) applications. Vomiting may be associated with licking the test substance. This does not appear to be exposure related. There were loose stools from two cats in the control group. Additionally, one male from the control group exhibited inappetence on days 22-24 and was observed to be circling and unsteady at the p.m. observation period on day 23. The clinical chemistry and hematology findings from this cat on day 22 were consistent with hemoconcentration due to dehydration. Possible cause of these signs was not

clear. His behavior and appetite were normal for the remainder of the study, as were his clinical pathology parameters. There were no other treatment related effects on hematology, coagulation or clinical chemistry parameters. There were no treatment related effects on body weight or food consumption, and there were no signs of irritation at the application sites.

Currently there is a product in the market with 9.1% Imidacloprid. The proposed product is adding 0.46% Pyriproxyfen to the current product. The added ingredient has low acute and chronic toxicity in mammalian species.

Any clinical signs on the study showed no consistent toxicological response. This study is classified as **Acceptable /Guideline** for a companion animal safety study (OPPTS 870.7200) in cats .

I. MATERIALS

A. Test material

9.1% Imidacloprid with 0.9% Pyriproxyfen (w/w) Spot-on Formulation (Advantage Plus® 9, and 18 for Cats)
Description: not provided
Lot No.: 99-901-66
Active Ingredients: Imidacloprid, 9.1% (w/w); Pyriproxyfen, 0.9% (w/w)
Storage Conditions: in the dark in a closed cabinet at room temperature

B. Administration: Topical (spot-on)

C. Vehicle and/or positive control

The control animals received the vehicle.

D. Test animals

Species: Cat
Breed: Domestic shorthair
Age and weight at study initiation: 7-12 months; males: 3.8-5.1 kg., females: 2.4-3.1 kg
Source: Liberty Research Inc., 170 Route 17C, P.O. Box 107, Waverly, New York
Housing: Individually in cages with approximately 7.5 square feet of floor space
Diet: Commercial feed purchased from Harlan Teklad, Madison, Wisconsin, once daily
Water: Tap water, *ad libitum*
Environmental conditions:
Temperature: not reported
Humidity: not reported
Air changes: not reported
Photoperiod: not reported
Acclimation period: 14 days

II. STUDY DESIGN

A. In life dates: start: August 11, 1999; end: September 21, 1999

B. Animal assignment/ Dosage and Administration

Cats were assigned to the groups in Table 1 using stratified blocked randomization according to weight. Group 1 received the test substance at 5X the label specified use volume, and group 2 received the vehicle without the two active ingredients at a volume equivalent to the 5X use rate volume of the test substance. The dose volume was 2.0 mL for cats of either group weighing less than or equal to 4.1 kg (9 lbs) and 4.0 mL for cats of either group weighing greater than 4.1 kg. Treatments were applied on the back, from the back of the head to the shoulder. Animals were dosed on Study Days 0, 7, 14, and 21. Dose volumes for treatments on study days 0 and 7 were determined using body weights from study day -1, and dose volumes for treatments on study days 14 and 21 were determined using body weights from study day 13.

TABLE 1. Study design

Group	Number of animals		Dose volume (mL)/multiple of recommended dose		Number of applications[a]
	Male	Female	Body weight≤9 lbs	Body weight>9 lbs	
1. Test substance	6	6	2.0 /5X	4.0/5X	4
2. Vehicle control	6	6	2.0 /5.6X	4.0/5.6X	4

Data taken from pp. 12-13, 16-17, MRID 45097001.

[a] Treatments were given on study days 0, 7, 14, and 21.

C. Dose selection rationale

The study was conducted as a limit test using 5 times the label specified, the recommended dose volume. The product was dosed according to weight in the following pre-measured dose volumes: 0.4 mL for cats weighing ≤9 lbs (4.1 kg) and 0.8 mL for cats weighing > 9 lbs. (4.1kg). The vehicle control group received the vehicle at dose volumes equal to 5 times the recommended use volumes of the test substance, which are equivalent to 5.6 times the usual use volumes of the vehicle. The product is intended for once a month use; however, the label states that "if re-treatment becomes necessary earlier than four weeks, do not re-treat more than once weekly." The study therefore included repeated treatments at weekly intervals for a total of four treatments.

D. Experimental design

The cats were observed daily during study days -14 through -1 (the acclimation period), and twice daily during study days 0 through 37 except on dosing days, when the animals were observed once prior to dosing and 4 times, approximately 1 hour apart, following dosing. These observations included evaluation of the "clinical condition" of the eyes,

appetite, feces, respiration, behavior changes, locomotion and musculature, skin, including dermal irritation, and any signs of vomiting. Physical examinations were conducted prior to the acclimation period and on study days -1 and 37. Body weights were recorded on study days -14, -7, -1, 13, 28, and 37. Food consumption was evaluated once daily during the acclimation period and twice daily during the study except on dosing days, when it was evaluated 5 times; in all cases, a daily summary of food consumption was also made. The amount of food consumed was estimated visually and scored as 1, 2, or 3, indicating, respectively, that greater than or equal to 75%, 25-75%, or less than 25% of the food was consumed; however, the quantity of food the animals were given was not provided in the report.

E. Pathological parameters

Baseline blood samples were collected on study days -7 and -1, and post-treatment blood samples were collected on study days 1, 22, and 37. The report did not mention the venipuncture sites used or whether the animals were fasted overnight prior to blood collection. Due to clotting of some blood samples, it was necessary to collect and test additional samples. Where necessary, study day 1 sampling and testing were repeated on study 8, study day 22 blood sampling and testing were repeated on day 23, and study day 37 blood sampling and testing were repeated on study days 41 and 42. The CHECKED (X) parameters were examined.

a. Hematology

X		X	
X	Hematocrit (HCT)*	X	Leukocyte differential count*
X	Hemoglobin (HGB)*	X	Mean corpuscular HGB (MCH)*
X	Leukocyte count (WBC)*	X	Mean corpusc. HGB conc.(MCHC)*
X	Erythrocyte count (RBC)*	X	Mean corpusc. volume (MCV)*
X	Platelet count		Reticulocyte count
	Blood clotting measurements		
	(Thromboplastin time)		
	(Clotting time)		
X	(Prothrombin time)*		
X	(Activated partial thromboplastin time)*		
	Erythrocyte morphology		

*Recommended in OPPTS 870.7200 Guidelines.

b. Clinical chemistry

X	ELECTROLYTES	X	OTHER
X	Calcium*	X	Albumin*
X	Chloride*	X	Blood creatinine*
	Magnesium	X	Blood urea nitrogen*
X	Phosphorus*		Total Cholesterol
X	Potassium*	X	Globulin*
X	Sodium*	X	Glucose*
		X	Total and direct bilirubin*
	ENZYMES	X	Total serum protein (TP)*
X	Alkaline phosphatase(ALK)*		Triglycerides
	Cholinesterase(ChE)		Serum protein electrophoresis
	Creatine kinase		Albumin/Globulin ratio
	Lactic acid dehydrogenase(LDH)	X	Calcium/phosphorus ratio
X	Serum alanine amino- transferase (also SGPT)*	X	Blood urea nitrogen/creatinine ratio
X	Serum aspartate amino- transferase(also SGOT)*	X	Sodium/potassium ratio
	Gamma glutamyl transferase(GGT)		
	Amylase		
	Glutamate dehydrogenase		

*Recommended in OPPTS 870.7200 Guidelines.

F Statistics

Baseline clinical pathology values were calculated for each animal by averaging the pre-treatment measurements, and study day -1 body weights were used as baseline. Body weight data were analyzed by first comparing the baseline body weights of the two groups by sex with a two-sample t-test. Body weight changes from baseline were calculated for each post-treatment day (study days 13, 20, 28, and 37), and body weight changes were then analyzed by sex with a repeated measure analysis of covariance including terms for Group, Animal (random), Day, and Group*Day interaction with baseline body weight as the covariate. Clinical pathology data were analyzed using a multivariate repeated measures ANOVA, including terms for Group, Sex, Animal (random), Day, and Group*Day interaction. If the Sex effect was statistically significant at the 0.10 level, the data were analyzed by sex with a multivariate repeated measures ANOVA including terms for Group, Animal (random), Day, and Group*Day interaction. If the Group*Day interaction was statistically significant at the 0.10 level, the data were graphed to investigate the nature of the Group by Day interaction, and the data for each study day were compared with normal ranges.

G. Disposition of animals

Not reported.

H. Compliance

Signed and dated Quality Assurance, Data Confidentiality, and Good Laboratory Practice Statements were present.

III. RESULTS

A. Exposure levels

Each 1.0 mL of the product contained 100 mg of imidacloprid and 10 mg of pyriproxyfen. For thirty days efficacy, the minimum desired efficacious dose for imidacloprid is 10 mg/kg, and the desired minimum efficacious dose for pyriproxyfen is 0.5 mg/kg. In terms of desired minimum efficacious doses in mg/kg, the exaggerated doses used in the study ranged from 4.92X to 9.57X for imidacloprid and 9.84X to 19.13X for pyriproxyfen.

B. Mortality

There were no deaths during the study.

C. Clinical signs

Clinical observations are summarized in Table 2. Within an hour following the initial treatment on study day 0, four cats in the test substance group and one cat in the vehicle control group were observed to be salivating, and at two hours post dosing all had recovered. The study author stated that "all the cats that salivated were due to licking the test material." Two males in the test substance group vomited, one on study day 19 and the other on study day 25. Two males in the vehicle control group had loose stools, one on study days 18 and 20, and the other on study day 33. One cat in the vehicle control group was observed to be unsteady and circling during the p.m. observation period on study day 23. By the a.m. observation period on study day 24, he had recovered but exhibited a rough hair coat condition at the application site. No mention was made of the study veterinarian examining this animal during the time he was exhibiting symptoms. On study days 14 and 21, rough hair coat was noted at the application sites of all cats of both groups 1-4 hours post dosing, and, on study day 21, one female from the test substance group was pruritic at one hour after dosing, with recovery by 2 hours after dosing. There were no observations of erythema, edema, or alopecia at the application sites. One cat in the vehicle control group exhibited ocular discharge on study day -9 (during acclimation) and study day 16; since this condition occurred both before and after treatment, it is unlikely to be treatment related.

TABLE 2. Clinical observations of cats treated with Imidacloprid/Pyriproxyfen Spot-on Formulation		
Treatment group	**Day**	**Observation**
1. Test substance	0	Salivation in 3 males and 1 female within an hour of dosing
	14	Rough hair coat condition at the dose site in 6 males and 6 females at the post dosing observation periods at 1-4 hours post dosing
	16	Ocular discharge in one female cat at the a.m. observation period[a]
	19	Vomiting by one male cat (#762) at the a.m. observation period
	21	Rough hair coat condition at the dose site in 6 males and 6 females at the post dosing observation periods at 1-4 hours post dosing; Pruritis in one female at 1 hour post dosing
	25	Vomiting by one male cat (#758) at the p.m. observation period
2. Vehicle control	0	Salivation in one female within an hour of dosing
	14	Rough hair coat condition at the dose site in 6 males and 6 females at the post dosing observation periods at 1-4 hours post dosing
	18	Loose stools in one male cat (#764)
	20	Loose stools in one male cat (#764)
	21	Rough hair coat condition at the dose site in 6 males and 6 females at the post dosing observation periods at 1-4 hours post dosing
	23	One male (#744) was circling and unsteady at the p.m. observation
	24	Rough hair coat condition at the dose site in one male (#744)
	33	Loose stools in one male cat (#749)

Data taken from Tables 6A and 6B, pp. 34-35, MRID 45097001.
[a] This cat also exhibited ocular discharge on study day -9, during acclimation.

D. Bodyweight and weight gain

Individual body weights of the cats fluctuated throughout the acclimation and treatment periods, with no consistent pattern being observed. Mean body weights of both groups, with the sexes both combined and separated, increased at each consecutive weighing from study day -1 to study day 37. There were no significant differences between groups for post-treatment changes in body weight

E. Food consumption

All of the cats on the study generally consumed greater than or equal to 75% of their food. One female (#750) in the test substance group consumed between 25 and 75% of her food on study days -13, 12, 15-17, 19, and 30-33. One female (#751) in the vehicle control group consumed between 25 and 75% of her food on study days 13, 14, 16-18, 31-32. Three additional cats from the test substance group and one cat from the vehicle control group consumed 25-75% of their food for 1-3 days. Cat number 744 from the vehicle control group, who was observed to be circling and unsteady on study day 23, consumed less than 25% of his food on study day 22 and 25-75% of his food on study days 23 and 24. All of the previously mentioned animals consumed greater than or equal

to 75% of their food during the remainder of the pre-treatment and treatment intervals. The study report did not include the quantities of food the cats were fed.

F. Hematology

Nine of the samples submitted for complete blood count and three of the samples submitted for coagulation measurements were could not be analyzed due to clotting. Additional samples were collected and tested as follows: study day 1 sampling and testing were repeated on study day 8; study day 22 sampling and testing were repeated on study day 23; and study day 37 sampling and testing were repeated on study days 41 and 42. Statistical analyses were conducted both with and without the data from the repeated tests, and wherever statistical significance was present without data from the repeated tests, it was also present when the data from the repeated tests was included. The individual results from these repeated tests were omitted from the study report although these data were included in calculating means and standard deviations. Statistically significant ($p<0.10$) Group by Day interactions were found for the following parameters: platelet counts for males, erythrocyte counts for females, and activated partial thromboplastin times, leukocyte, eosinophil, and lymphocyte counts, and mean corpuscular volumes for the pooled sexes. These values are given in Table 3. These values were all within pre-treatment ranges, and the changes were considered to be spontaneous in nature and unrelated to treatment.

On study day 22, cat #744 (the cat that was observed to be circling and unsteady on study day 23) exhibited an increased hematocrit, erythrocyte count, and hemoglobin concentration. These values were all outside the pre-treatment ranges for these parameters. (See G. Clinical chemistry below.)

TABLE 3. Hematology and coagulation parameters in cats treated with Imidacloprid/Pyriproxyfen Spot-on Formulation which exhibited statistically significant (p<0.10)Changes, Group by Day interactions [a]								
Parameter	1. Test substance				2. Controls			
	Baseline [b]	Day 1[c]	Day 22[d]	Day 37[e]	Baseline	Day 1[f]	Day 22[g]	Day 37[h]
Males								
Platelets ($10^6/\mu L$)	0.33	0.26	0.34	0.39	0.30	0.29	0.34	0.33
Females								
Erythrocytes ($10^6/\mu L$)	9.71	8.73	8.48	8.85	8.46	7.86	8.35	8.65
Pooled Sexes								
Activated partial thromboplastin time (sec)	12.68	13.03	12.21	12.28	13.53	12.80	12.94	13.34
MCV (fl)	41.33	41.19	41.34	41.47	42.81	43.08	43.27	42.85
Leukocytes ($10^3/\mu L$)	15.05	14.84	11.44	11.99	13.74	15.07	13.12	10.24
Eosinophils ($10^3/\mu L$)	0.81	1.10	0.43	0.43	0.93	0.90	0.65	0.39
Lymphocytes ($10^3/\mu L$)	6.22	5.44	4.04	5.13	4.68	4.63	3.87	3.26

Data taken from Tables III.1 and III.2, pp. 81-82, MRID 45097001

[a] Mean values

[b] Baseline values are the means of results from study days -7 and -1.

[c] Means for complete blood count (CBC) parameters include data from Day 8 for one female.

[d] Means for CBC parameters include data from Day 23 for one male.

[e] Means for CBC parameters include data from Day 40 or 41 for two males and two females.

[f] Means for CBC parameters include data from Day 8 for two females and one male. Means for coagulation parameters include data from Day 8 for one female.

[g] Means for CBC parameters include data from Day 23 for one female

[h] Means for coagulation parameters include data from Day 40 or 41 for one male.

G. Clinical chemistry

Statistically significant ($p<0.10$) Group by Day interactions were found for the following clinical chemistry parameters: alkaline phosphatase and BUN/Creatinine ratio in males. These values were within the pretreatment ranges, and the changes were considered to be spontaneous in nature and unrelated to treatment.

On study day 22, cat #744 (the cat that was observed to be circling and unsteady on study day 23) exhibited increased sodium concentration and total protein; both these values exceeded the pre-treatment ranges. There were also slight increases in his BUN on study

days 1 and 37 and creatinine. These findings in conjunction with those mentioned above (see F. Hematology) are consistent with hemoconcentration due to dehydration.

TABLE 4. Clinical chemistry parameters in cats treated with Imidacloprid/Pyriproxyfen Spot-on Formulation which exhibited statistically significant ($p<0.10$) Group by Day interactions [a]

Parameter	1. Test substance				2. Controls			
	Baseline	Day 1	Day 22	Day 37	Baseline	Day 1	Day 22	Day 37
Males								
Alkaline phosphatase activity (u/L)	52.92	48.33	48.50	45.50	48.92	52.00	53.17	39.00
BUN/creatinine ratio	18.86	18.43	17.56	19.60	18.29	18.33	19.77	18.73

Data taken from Tables III.I, p. 81, MRID 45097001.
[a] Mean values

H. Necropsy findings

Necropsies and histopathological examinations were not performed, as all animals survived until termination of the study, and no animals displayed clinical signs which were considered to warrant necropsy.

IV. DISCUSSION

A. Treatment related clinical signs included salivation and a rough hair coat appearance at the treatment site. Four cats from the test group and one from the control group exhibited salivation after the first treatment. Salivation was first noted within an hour of dosing and ended before the 2 hour post-treatment observation period. The study author attributed the salivation to the animals licking the test substance or vehicle. A rough hair coat appearance at the application site was noted for all cats in both groups on study days 14 and 21 during all post-treatment observations, and one animal from the test group was pruritic at one hour post dosing on study day 21. Clinical signs that may have been related to treatment included vomiting by two cats in the test group and loose stools from two cats in the (vehicle) control group. Additionally, one male from the control group exhibited inappetence on study days 22-24 and was observed to be circling and unsteady at the p.m. observation period on day 23. Clinical chemistry and hematology findings from this cat on day 22 were consistent with hemoconcentration due to dehydration (elevated hematocrit, erythrocyte count, hemoglobin, BUN, creatinine, sodium, and total protein), but since this cat was apparently not given a physical examination, it is unknown whether he was clinically dehydrated, febrile, or presenting neurological deficits. His behavior and appetite were normal for the remainder of the study, as were his clinical pathology parameters. There were no other treatment related effects on hematology, coagulation, and clinical chemistry parameters. There were no

treatment related effects on body weights or food consumption, and there was no evidence of irritation at the application sites. Since the cat that exhibited inappetence, circling, and unsteadiness following the fourth treatment was in the control group, these clinical signs were clearly not due to toxic effects from the active ingredients of the product; however, they may represent toxic effects from an ingredient in the vehicle. The animal was not examined more closely. However, the signs were transient, and the animal apparently recovered with no clinical signs for the remainder of the study and no abnormal physical examination findings on study day 37. The guideline only requires a single re-treatment with observation of the animals to continue only 14 days beyond treatment if no clinical signs of toxicity are noted. As the clinical signs in question did not occur until day 22, (exactly 15 days after the second treatment and were exhibited by an animal from the vehicle control group), they are not considered to be a treatment related.

B. Study deficiencies

An animal on the study exhibited clinical signs which needed a thorough examination to determine the possible cause of such clinical signs.

Due to clotting of some blood samples, it was necessary to collect and test additional samples. Where necessary, study day 1 sampling and testing were repeated on study 8, study day 22 blood sampling and testing were repeated on day 23, and study day 37 blood sampling and testing were repeated on study days 41 and 42. Individual data from the repeated tests were not included in the study report. The guideline requires clinical pathology testing 24 hours after treatment with additional assessment on day 7 if the day 1 results are altered. It is unclear why the tests on day 1 were not repeated until day 8.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SEP - 7 2000

Mr. F. Terry McNamara
Bayer Corporation
Animal Health, Agriculture Division
P.O. Box 390
Shawnee Mission, KS 66201

Subject: Applications for New Advantage Products
Tox and Animal Safety Studies
Reg Nos. For Tox Studies: 11556-REO, REI, RET, REL, REA
Reg NO. For ASS: 11556-11556-RGN
Your submission date, April 7, 2000

Dear Mr. McNamara:

Just a note to let you know that we are coming to a close with reviewing your six new product applications for Advantage. Enclosed is a copy of one completed animal safety study review and five tox study reviews. To complete the reviews, five animal safety study reviews are need. Upon completion, I will notify you as to when you can commence with label changes needed to satisfy registration of your products. If there are questions, call me 703 305-5409.

Sincerely,

Dani Daniel
Insecticide-Rodenticide Branch
Registration Division 7505C

Enclosure:

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND
TOXIC SUBSTANCES

August 30, 2000

MEMORANDUM

EPA File Symbol: 11556-REA Advantage® Plus 9 for Cats
DP Barcode: D265764
Case No: 068807
PC Codes: 129099 Imidacloprid; 129032 Pyriproxyfen

From: Byron T. Backus, Ph.D., Toxicologist
Technical Review Branch
Registration Division (7505C)

Byron T. Backus 8/30/2000

To: Helene Daniel/Tina Levine, PM 04
Insecticide-Rodenticide Branch
Registration Division (7505C)

Registrant: Bayer Corp.

ACTION REQUESTED: Review a six-pack of acute toxicity studies. These studies are being used to support the proposed registrations of 6 products, which will be used to control fleas on domestic animals. The MRID numbers of these studies are 45096904 through 45096909.

COMMENTS AND RECOMMENDATIONS: The six acute toxicity studies have all been classified as acceptable, and the proposed product, EPA File Symbol 11556-REA

(ADVANTAGE PLUS 9 FOR CATS) has the following acute toxicity profile:

Acute Oral LD50	III	Acceptable
Acute Dermal LD50	IV	Acceptable
Acute Inhalation LC50	IV	Acceptable
Primary Eye Irritation	III	Acceptable
Primary Dermal Irritation	IV	Acceptable
Dermal Sensitization	No	Acceptable

These studies were conducted on a formulation containing 9.1% Imidacloprid and 0.9% Pyriproxyfen. The proposed product has a label declaration of 9.1% Imidacloprid and 0.46% Pyriproxyfen, with 90.44% inert ingredients.

It is emphasized that there are additional studies (companion animal safety studies) which have been submitted in support of the registration of this product. These companion animal safety studies should be reviewed and classified as acceptable before this product is registered.

Since the Oral LD_{50} value is below 1500 mg/kg, and this product has residential uses, then it will require Child Resistant Packaging (CRP).

The following is the precautionary labeling for this product, based on the acute toxicity profile given above, and as obtained from the Label Review System:

Date: 08/30/00 LABEL REVIEW SYSTEM

ID #: 011556-00126 Advantage Plus 9 for Cats

SIGNAL WORD: CAUTION

PRECAUTIONARY STATEMENTS:

Harmful if swallowed. Causes moderate eye irritation. Avoid contact with eyes or clothing.

STATEMENT OF PRACTICAL TREATMENT (SOPT):

IF SWALLOWED: Call a poison control center or doctor immediately for treatment advice. Have person sip a glass of water if able to swallow. Do not induce vomiting unless told to by a poison control center or doctor. Do not give anything by mouth to an unconscious person.

IF IN EYES: Hold eye open and rinse slowly and gently with water for 15-20 minutes. Remove contact lenses, if present, after the first 5 minutes, then continue rinsing eye. Call a poison control center or doctor for treatment advice.

NOTE TO PHYSICIAN:

Note to PM/CRM/Registrant: The proposed label should contain a "Note to Physician." The following statements are suggested types of information that may be included, if applicable:

- technical information on symptomatology;
- use of supportive treatments to maintain life functions;
- medicine that will counteract the specific physiological effects of the pesticide;
- company telephone number to specific medical personnel who can provide specialized medical advice.

DATA REVIEW FOR ACUTE ORAL TOXICITY TESTING (870.1100, formerly §81-1))

Product Manager: 04
MRID No.: 45096904

Reviewer: Byron T. Backus, Ph.D.
Study Completion Date: September 30, 1999
Study No.: 99-A12-DZ

Testing Facility: Bayer Corporation, Agriculture Division Toxicology, Stilwell, Kansas
Author: Sturdivant, D.W.

Quality Assurance (40 CFR §160.12): Included (p. 6-7)

Test Material: Imidacloprid (9.1%)/Pyriproxyfen (0.9%) Spot On; a clear yellow to light brown liquid, Lot No. 99-625-41

Species: Rat; Wistar Hannover (Crl:WI(GIx/BRL/Han)IGS BR
Age: Young adult (Males: 9-10 weeks; Females: approximately 12 weeks)
Weight: Males: 194-242 g; Females: 159-207 g
Source: Charles River Laboratories, Raleigh, NC

Conclusion:

1. **LD_{50} (mg/kg):**
   Males: = 1283 (95% C.L: 680-1678) mg/kg
   Females: = 1000 (95% C.L: not calculable) mg/kg
   Combined: = not reported
2. **The estimated LD_{50} is** = 1000 mg/kg
3. **Tox. Category:** III **Classification:** Acceptable

Procedure (including deviations from 870.1100): "Groups of six male and six female rats were treated by gavage at varying concentrations of Imidacloprid (9.1%)/Pyriproxyfen (0.9%) Spot On in vehicle (deionized water/PEG 200 1:1 v/v)." Groups of male rats were treated at nominal doses of 1000, 1500 and 2000 mg/kg while groups of female rats were treated at nominal doses of 500, 1000 and 2000 mg/kg... "Six male and six female rats were dosed with vehicle and served as concurrent control groups."

Results:

Dosage (mg/kg)[a]	Number of Deaths/Number Tested		
	Males	Females	Combined
0	0/6	0/6	0/12
500	-	0/6	-
1000	1/6	3/6	4/12
1500	5/6	-	-
2000	5/6	6/6	11/12

[a]Average actual doses were 0, 1038, 1542 and 2145 mg/kg for males and 0, 614, 1027 and 2071 mg/kg for females.

Observations: There were no clinical signs of toxicity in the females dosed at 500 mg/kg. Symptoms at 1000 mg/kg included: brown nasal staining, brown oral staining, decreased activity, tremors and (females only) urine staining. Symptoms at 1500 and 2000 mg/kg included ataxia, decreased activity and tremors. Mortalities, when they occurred, were on days 0 to 2.

Gross Necropsy: "The following compound-related gross observations were observed at necropsy only in animals that were found dead: salivation and nasal discharge in males and females, red discolored lungs and urine in males. There were no gross observations noted in females from the 500 mg/kg dose group or in males from the 1000 mg/kg dose group. Also, there were no gross observations noted in any surviving, treated male or female rats or in control male or female rats.

DATA REVIEW FOR ACUTE DERMAL TOXICITY TESTING (870.1200, formerly §81-2)

Product Manager: 04
MRID No.: 45096905

Reviewer: Byron T. Backus, Ph.D.
Study Completion Date: September 30, 1999
Study No.: 99-A22-EA

Testing Facility: Bayer Corporation, Agriculture Division Toxicology, Stilwell, Kansas
Author: Sturdivant, D.W. and Berry, L.A.

Quality Assurance (40 CFR §160.12): Included (p. 6-7)

Test Material: Imidacloprid (9.1%)/Pyriproxyfen (0.9%) Spot On; a clear yellow to light brown liquid, Lot No. 99-625-41

Species: Rat; Wistar Hannover (Crl:WI(GIx/BRL/Han)IGS BR
Age: Young adult (Males: approximately 9 weeks; Females: approximately 12 weeks)
Weight: Males: 192-245 g; Females: 174-210 g
Source: Charles River Laboratories, Raleigh, NC

Dermal LD_{50} Testing:

Conclusion:

1. **LD_{50} (mg/kg):**
   Males: > 5000 mg/kg (0/6 died)
   Females: > 5000 mg/kg (1/6 died)
   Combined: > 5000 mg/kg (1/12 died)
2. **The estimated LD_{50} is** > 5000 mg/kg
3. **Tox. Category:** IV **Classification:** Acceptable

Procedure (including deviations from 870.1200): "Hair from the dorsal and lateral areas of the trunk...was removedon the day prior to dose application... Groups of six males and six females each received a single dose of either 0 (deionized water) mg/kg or 5000 mg of the undiluted test substance/kg of body weight. For the animals treated with the Imidacloprid (9.1%)/Pyriproxyfen (0.9%) Spot On, measured aliquots of the undiluted test substance were applied uniformly... directly to the shaved area of the animal's back and then a plastic-backed, two-ply gauze patch... was used to cover the dosed area... The gauze patch was held in place with hypoallergenic tape. The animal was then wrapped with an elastic bandage, which was also secured with tape. After a minimum of 24 hours, the bandages and patch were removed and the dose site was wiped using paper towels dampened with tap water to remove as much test substance residue as feasible without inducing skin damage..."

Results:

Dosage (mg/kg)	Number of Deaths/Number Tested		
	Males	Females	Combined
0	0/6	0/6	0/12
5000	0/6	1/6	1/12

Observations: "One female from the 5000 mg/kg dose group...was found dead on post-

treatment day 2... Clinical signs of red lacrimal staining, nasal staining, fecal and urine staining in males and females are considered to be unrelated to treatment with the test substance since they occurred at a comparable incidence in control and treated animals. These signs as well as ungroomed appearance in two control males are ascribed to the manipulation and subsequent wrapping of the animal that is associated with dermal exposure and/or the use of Elizabethan collars... Compound-related clinical signs of decreased activity, labored breathing, and rales were observed in one treated female which died on post-treatment Day 2."

Gross Necropsy: "There were no compound-related gross observations noted at necropsy for the males or females that survived until terminal sacrifice. Observations of nasal discharge and urine stained ventrum were observed in one treated female that was found dead on post-treatment Day 2 and were considered compound-related."

DATA REVIEW FOR ACUTE INHALATION TOXICITY TESTING (870.1300, formerly §81-3)

Product Manager: 04
MRID No.: 45096906

Reviewer: Byron T. Backus, Ph.D.
Study Completion Date: October 25, 1999
Study No.: 99-A42-EB

Testing Facility: Bayer Corporation, Agriculture Division Toxicology, Stilwell, Kansas
Author: Sturdivant, D.W.

Quality Assurance (40 CFR §160.12): Included (p. 6-7)

Test Material: Imidacloprid (9.1%)/Pyriproxyfen (0.9%) Spot On; a clear yellow to light brown liquid, Lot No. 99-625-41

Species: Rat; Wistar Hannover (Crl:WI(GIx/BRL/Han)IGS BR
Age: Young adult (Males: approximately 9 weeks; Females: approximately 12 weeks)
Weight: Males: 207-270 g; Females: 192-217 g

Source: Charles River Laboratories, Raleigh, NC

Conclusion:

1. **LC_{50} (mg/L):**
   Males: > 2.50 mg/L (0/6 died)
   Females: > 2.50 mg/L (0/6 died)
   Combined: > 2.50 mg/L (0/12 died)
2. **The estimated LC_{50} is** > 4.21 mg/L
3. **Tox. Category:** IV **Classification**: Acceptable

Procedure (including deviations from 8700.13): Exposure was for four hours, and was nose-only. "The test substance was generated as a liquid aerosol with a respirable particle size distribution."

Exposure Concentration ± S.D. mg/L (Analytically Determined)	Number of Deaths/Number Tested		
	Males	Females	Combined
0[a]	0/6	0/6	0/12
2.50 ± 1.10	0/6	0/6	0/12

[a]A group of 6 male and 6 female rats was "shamp-exposed to conditioned air via the nose-only route for a single four-hour period."

Clinical Observations: There were no deaths. "Clinical signs observed during this study were red perigenital staining, fecal staining and ungroomed appearance and were observed only on Day 0. Although the incidence of these signs was slightly higher in animals exposed to the test substance than air-control animals, they are considered a result of restraint during the exposure period and are not considered compound-related."

Gross Necropsy Findings: "No gross observations were observed at necropsy during this study."

Chamber Atmosphere			
Analytical Concentration	**Nominal Concentration**	**MMAD (µm)**	**GSD**
2.50 mg/L	3.20	2.61	3.02

59% of the particle mass was less than 4 µm, and 26% was less than 1 µm. These percentages are the means of 5 samples.

Other Information:

Chamber Environment [a]	
Chamber Volume	27 L
Airflow (exhaust flow rate)	28 LPM
Mean Chamber Temperature	23.5 °C
Relative Humidity	81%[a]

[a]The high relative humidity is attributed to a high percentage of water contained in the test substance formulation.

DATA REVIEW FOR PRIMARY EYE IRRITATION TESTING (870.2400, previously §81-4)

Product Manager: 04
MRID No.: 45096907
Sponsor Study No.: 99C-I35-FG

Reviewer: Byron T. Backus, Ph.D.
Study Completion Date: November 19, 1999
Study No.: Covance 90801932

Testing Facility: Covance Laboratories Inc., Madison, WI 53704
Author: Glaza, S.M.

Quality Assurance (40 CFR §160.12): Included (p. 4)

Test Material: Imidacloprid (9.1%)/Pyriproxyfen (0.9%)/5.0% Water Spot On; a clear, light-yellow liquid, Lot No. 99-901-73
Dosage: 0.1 mL
Species: Rabbits; Albino, Hra(NZW) SPF strain
Age: approximately 16 weeks of age
Weight: 2.57-2.707 kg
Source: Covance Research Products Inc., Kalamazoo, MI
Conclusion:

1. **Toxicity Category:** III
2. **Classification**: Acceptable

Procedure (including deviations from 870.2400): Three rabbits were used. "The test substance was administered as received... Initially one animal was treated and the results evaluated. Based on the irritation observed, the other two animals were then treated in the same manner. Each rabbit received 0.1 mL of the undiluted test substance placed into the everted lower lid of the right eye... The upper and lower lids were gently held together for 1 second to prevent loss of material and then released. The eyes of the rabbits remained unflushed immediately after treatment."

Observations	Number "positive"/number tested						
	Hours				Days		
	1	24	48	72	4	7	14
	Unwashed eyes						
Corneal Opacity	3/3	3/3	3/3	3/3	1/3	0/3	0/3
Iritis	3/3	3/3	3/3	2/3	1/3	0/3	0/3
Conjunctivae:							
Redness[1]	3/3	3/3	3/3	3/3	2/3	0/3	0/3
Chemosis[1]	3/3	3/3	3/3	2/3	0/3	0/3	0/3
Discharge[1]	3/3	2/3	3/3	2/3	0/3	0/3	0/3

[1]Score of 2 or greater considered as a positive effect.

"Sodium fluorescein examinations were used to aid in revealing possible corneal injury at the observations conducted at 24, 48, 72, and 96 hours and Day 7 or until a negative response for

that animal was obtained."

Summary: "All 3 animals showed excessive pawing at the treated eye after test substance installation, and one animal vocalized following test substance instillation. All eyes had cleared by day 7 except for grade "1" conjunctival redness (not considered a positive response) in all 3 eyes; at day 14 all scores were zero.

DATA REVIEW FOR DERMAL IRRITATION TESTING (870.2500, previously §81-5)

Product Manager: 04
MRID No.: 45096908
Sponsor Study No.: 99C-I25-DL

Reviewer: Byron T. Backus, Ph.D.
Study Completion Date: October 6, 1999
Study No.: Covance 90503024

Testing Facility: Covance Laboratories Inc., Madison, WI 53704
Author: Glaza, S.M.

Quality Assurance (40 CFR §160.12): Included (p. 4)

Test Material: Imidacloprid (9.1%)/Pyriproxyfen (0.9%)/5.0% Water Spot On; a clear, light-yellow liquid, Lot No. 99-625-41

Dosage: 0.5 mL
Species: Rabbit; albino, HRA:(NZW)SPF
Age: approximately 15 weeks old
Weight: 2.308-2.554 g
Source: Covance Research Products Inc., Kalamazoo, MI

Conclusion:

1. **Toxicity Category:** IV
2. **Classification**: Acceptable

Procedure (including deviations from 870.2500): Three rabbits were used. "The undiluted test substance was applied to the intact skin site on each animal's back (approximate exposure area 6.25 cm^2) in the amount of 0.5 mL. Each area of application was covered with an 8-ply 2.5-cm x 2.5-cm gauze patch secured with paper tape, loosely overwrapped with Saran Wrap®, and secured with Elastoplast® tape to provide a semiocclusive dressing... At the end of the 4-hour exposure period, the patches were removed and the test sites were washed using liquid Ivory® soap mixed with water, rinsed with water, and dried with disposable paper towels. Any residual test substance was removed from the test sites as thoroughly as possible without irritating the skin."

Results: All scores (4, 24, 48 and 72 hrs) for erythema and edema were zero. The PII = 0.0

DATA REVIEW FOR DERMAL SENSITIZATION TESTING (870.2600, formerly §81-6)

Product Manager: 04
MRID No.: 45096909
Sponsor Study No.: 99C-I24-DN

Reviewer: Byron T. Backus, Ph.D.
Study Completion Date: October 6, 1999
Study No.: Covance 90503026

Testing Facility: FMC Corporation Toxicology Laboratory, Princeton, NJ 08543
Author: Freeman, C.

Quality Assurance (40 CFR §160.12): Included (p. 4)

Test Material: Imidacloprid (9.1%)/Pyriproxyfen (0.9%)/5.0% Water Spot On; a clear, light-yellow liquid, Lot No. 99-625-41

Positive Control Material: alpha-hexylcinnamaldehyde
Species: Guinea pigs, albino; Crl:(HA)BR
Age: Young adult; 5-7 weeks of age at initiation of dosing
Weight: 375-468 g
Source: Charles River Laboratories, Inc., Kingston, NY
Method: modified Buehler

Conclusion:

1. **There is no indication that this product is a dermal sensitizer.**
2. **Classification**: Acceptable

Procedure (including deviations from 870.2600): A group of 20 guinea pigs (10M and 10F) were exposed to the test material during both induction and challenge, while an additional group of 10 (5M and 5F) served as the naive controls, and were exposed at challenge only. In the induction phase, "the undiluted test substance was applied to each animal in the test group by placing 0.4 mL on an adhesive patch (Hill Top Chamber®, 25-mm diameter) and placing the patch on the induction site along the dorsal anterior left quadrant. The patch was covered with dental dam and overwrapped with Elastoplast® tape. The dressing remained in place for a period of 6 hours after which it was removed. Any residual test substance was then removed from the application site using water and disposable paper towels.

The laboratory test system was validated by using alpha-hexylcinnamaldehyde as a positive control within the previous six months (positive control study completed August 4, 1999; study with Imidacloprid (9.1%)/Pyriproxygen (0.9%) Spot On was completed on October 6, 1999).

In the induction phase, 0.4 mL aliquots of the undiluted test material were applied using Hilltop Chambers, with 6-hour exposure periods. The animals in the test group received one application per week for a total of three applications. Challenge was 2 weeks after the last induction application with the same amount of test material at a previously unexposed site; in addition to the 20 animals which had been previously exposed, a group of 10 naive animals was similarly treated.

Results: There was no irritation (all scores were zero) at 24 hours following each induction application. At challenge, 2/20 previously induced animals, as well as 1/10 naive controls, showed a score of 0.5 at 24 hours. All animals (previously induced and naive control) scored 0 at 48 and 72 hrs following challenge treatment.

ACUTE TOX ONE-LINERS

1. **DP BARCODE:** D265764
2. **PC CODE:** 129099 Imidacloprid; 129032 Pyriproxyfen
3. **CURRENT DATE:** August 30, 2000
4. **TEST MATERIAL:** Imidacloprid (9.1%)/Pyriproxyfen (0.9%) Spot On; a clear yellow to light brown liquid, Lot No. 99-625-41 (used for all studies except primary eye irritation); Lot No. 99-901-73 (used for primary eye irritation)

Study/Species/Lab Study #/Date	MRID	Results	Tox. Cat.	Core Grade
Acute oral toxicity/rat/Bayer Corp. Toxicology/99-A12-DZ/SEP-30-1999	45096904	LD_{50} (M) = 1283 (95% C.L. 680-1678) mg/kg; LD_{50} (F) = 1000 (95% C.L. not calculable) mg/kg	III	A
Acute dermal toxicity/rat/Bayer Corp. Toxicology/99-A22-EA/SEP-30-1999	45096905	LD_{50} > 5000 mg/kg (0/6M, 1/6F females died following dosage at this level)	IV	A
Acute inhalation toxicity/rat/Bayer Corp. Toxicology /99A42-EB/OCT-25-1999	45096906	LC_{50} > 2.50 mg/L (males, females, combined). No mortalities following 4-hr exposure to this concentration.	IV	A
Primary eye irritation/rabbit/Covance Laboratories Inc./Covance 90801932/NOV-19-1999	45096907	Three eyes tested: All showed corneal opacity through 72 hrs. All eyes had cleared by day 7 except for grade "1" conjunctival redness (not considered a positive response) in all 3 eyes; at day 14 all scores were zero.	III	A
Primary dermal irritation/rabbit/ Covance Laboratories Inc./Covance 90503024/OCT-6-1999	45096908	All scores zero at 1, 24, 48 and 72 hrs. PII=0.00.	IV	A
Dermal sensitization/guinea pig/ Covance Laboratories Inc./Covance 90503026/OCT-6-1999	45096909	Not a sensitizer	–	A

Core Grade Key: **A =Acceptable, S = Supplementary, U = Unacceptable, V = Self Validated**

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

JUN 16 2000

Mr. F. Terry McNamara
Bayer Corporation
Animal Health, Agriculture Division
P.O. Box 390
Shawnee Mission, KS 66201

Subject: Application for New Cat Products
Advantage Plus 9 for Cats and Advantage Plus 18 for Cats
Reg Nos. 11556-REO and 11556-REA
Your submission date, April 7, 2000

Dear Mr. McNamara:

The labeling referred to above, submitted in connection with registration under the Federal Insecticide, Fungicide, and Rodenticide Act as amended is unacceptable for the reason listed below:

The product chemistry review for the above products have been completed. The chemist has determined that your submitted labels and confidential statements of formula contains a number of deficiencies that need to be addressed. However, the animal safety study reviews and the tox reviews are yet to be completed. Please hold off making any corrections to the labels. until you receive the entire package. Enclosed are copies of the product chemistry reviews to help guide you in correcting the labels and the confidential statements of formula. If there are questions concerning these reviews, call me at 703 305-5409.

Sincerely,

/s/

Dani Daniel
Insecticide-Rodenticide Branch
Registration Division 7505C

Enclosure:

DATE: 2/JUNE/2000

SUBJECT: PRODUCT CHEMISTRY REVIEW OF MP [ ] EP [X]
DP BARCODE No.:D265763 REG./File Symbol No.:11556-REA
PRODUCT NAME: Advantage Plus 9 for Cats
COMPANY: Bayer Corporation

FROM: Linda L. Kutney, Chemist
Product Chemistry Team
Technical Review Branch (TRB)/RD (7505C)

TO: Tina Levine/Dani Daniel, PM #4
Insecticide Branch/RD(7505C)

INTRODUCTION

The Bayer Corporation has applied for registration of six new insecticides intended to kill fleas on different sizes of cats and dogs. All six of these products contain identical confidential statements of formula, CSFs (dated 4-7-00)and separate proposed labels, also dated 4-7-00.

This review covers one of the six insecticides, the subject product named, Advantage Plus 9 for Cats, Once-A-Month Topical Flea Treatment for Cats and Kittens 7 Months and Older and 9 lbs. and Under, Reg. No. 11556-REA, which Bayer submitted a me-too application, based on their product Advantage 9, EPA Reg. No. #11556-116.

The subject Advantage Plus product differs from the older Advantage product in that it includes 0.46% of an insect growth regulator pyriproxyfen, added to help control flea eggs, and contains an additional inert. The subject product reportedly controls larval and adult fleas, as well as flea eggs, and is to be applied to the back of the neck or shoulders of the cat.

Bayer submitted the CSF and proposed label for the subject product and the studies entitled, "Imidacloprid/pyriproxyfen Spotton Formulation (containing 5% water) Product Chemistry," dated 11-22-99, MRID 450969-03, "Product Chemistry of (10%w/v, 9.1% w/w) Imidacloprid & (0.5% w/v, 0.46% w/w) Pyriproxyfen TopicalSolution -Product Identity, Composition and Analysis," dated 12-16-99, MRID 450969-02 and "Validation of Bayer Animal Health Test Method -TMC-14.02 for the Determination of Imidacloprid and Pyriproxyfen in the (10%w/v, 9.1% w/w) Imidacloprid & (0.5% w/v, 0.46% w/w) Pyriproxyfen Topical Solution Formulation by HPLC," dated 1-26-00, MRID 450969-01.

The subject product is a liquid containing two active

ingredients, a.i.'s, 9.10% imidacloprid (Reg. No. 3125-414,98.0%) and 0.46% pyriproxyfen [redacted] and 90.44% inert ingredients.

FINDINGS

TRB has reviewed this submission and reports the following findings:

- All of the inert ingredients are cleared for use in formulated pesticides.
- The CSF exceeds the limits for nominal, upper and lower limits of the a.i.'s (40CFR 158.175) and the nominal concentrations on the draft label and CSF are different.
- The inerts listed on the CSF do not include the name and address of the suppliers.
- The draft label contains appropriate storage and disposal instructions.
- The enforcement method (40CFR 158.180) is labeled "Confidential Business Information."
- Data requirements for product identity and composition (40CFR 158.155), production process (40CFR 158.162), formulation process(40CFR 158.165), impurities (40CFR 158.1670), description of materials used in production (40CFR 158.160), preliminary analysis (40CFR 158.170) and submittal of samples (40CFR 158.190) are satisfied.
- Group B Product chemistry requirements listed in Series 830 Guidelines under 40CFR 158.190 are satisfied with the exception of explodability (830-6315), Storage Stability of the Product (830-6317), and miscibility (830-6319).
- The subject product contains an a.i. and an impurity which is not present in the product Bayer wishes to "me-too," and the nominal concentrations and certified limits of the subject product and the product to be "me-too-ed" are different.
- The pH and density of the subject product and the product the me-too application is based on are different.

CONCLUSION

TRB has reviewed this submission and concludes the following:

- Because the nominal concentrations of a.i.'s on the CSF are not identical to the label concentrations, the Registrant should resubmit the CSF and label and ensure that the concentrations of the a.i.'s are correct and identical.

- The name and address of the suppliers of inerts should be included on a revised CSF.

- The enforcement analytical method (40CFR 158.180) will be satisfactory, providing the Registrant submits a new copy not labeled "Confidential Business Information." This is a 3-97 FIFRA requirement (Section 10 (d)(1))needed for enforcement purposes, etc.

- Group B Product chemistry requirements listed in Series 830 Guidelines under 40CFR 158.190 explodability (830-6315), Storage Stability of the Product (830-6317), miscibility (830-6319) and dielectric breakdown voltage (830-6321) have not been fulfilled and should be submitted.

- The subject product, Reg. No. 11556-REA, is not substantially similar to EPA's Reg. No. 11556-116, from a product chemistry point of view, because it contains an additional a.i. and inert ingredient, and because the nominal and certified limits of the components are not substantially similar (see the Confidential Appendix for details).

1. Reviewer: Linda L. Kutney

2. Company: Bayer Corporation

3. Type of Submission: Registration [X] Reregistration [ ]
New [X] Resubmission [ ] Amendment [ ] "ME-TOO" [X]
Alternate Formulation [ ] Experimental Use Permit [ ]
Other (Specify)

4. If "Me-TOO" Registration, this product is [ ] is not [X] similar or substantially similar to EPA's Reg. No.:
11556-116
If not, comment in Confidential Appendix on the significant differences between the registered and the new source.

CONFIDENTIAL STATEMENT OF FORMULA

5. Type of formulation and the sources of active ingredients:
• Non-integrated formulation system.....[X]
• Are all technical grade active ingredients used registered? • yes [X] • no [ ], If no, specify
• Integrated formulation system.....[ ]

6. Clearance of intentionally added ingredients in the formulation for the intended use (indicate in the Confidential Appendix those that are not cleared; the PC Codes should be provided by the chemist on the CSF for those that are cleared):

6(a) Formulation intended for food use under 40CFR§180.1001:
• yes [ ] • no [X] • Some are cleared, others are not [ ]
Cleared under list: • c[ ] • d[ ] • e [ ]

Are there any limitations for use as an inert under 40CFR§180.1001?

• yes [ ] • no [X], If yes, specify

6(b) Formulation intended for non-food use:
• yes [X] • no [ ] • Some are cleared, others are not [ ]

6(c) Clearance by the FDA of certain formulations under 21CFR§170 to 199,e.g.,(a) indirect food additives, such as food contact surface sanitizers; adhesives, coatings, paper and paperboard products that may contact food in packaging or holding; & (b) substances generally recognized as safe,GRAS
• yes [ ] • no [X] • Some are cleared, others not [ ]
If yes, the entire formulation is cleared under 21CFR§

7. The density, pH, and flammability values given on the CSF are identical with those of GRN 830.7300(density), 830.7000(pH), and 830.6315(Flammability), respectively:
● yes [X] ● no [ ]

8. The nominal concentrations (NC) of the active ingredients and the upper and lower certified limits (UCL & LCL) are as follows:

		% by weight		
Active ingredient(s)	REG-NO	NC	UCL	LCL
Imidacloprid	3125-414	8.9	9.3	8.4
Pyriproxyfen	[redacted]	0.45	0.50	0.40

9. The calculated NCs, based on the pure active ingredients (PAI), are identical to those on the label:
● yes [ ] ● no [X]
Not acceptable for imidacloprid and Pyriproxyfen-as required in PR Notice 91-2

10. The certified limits are within the standard limits as per 40CFR§158.175 or are adequately explained if different:
● yes [ ] ● no [X]

PRODUCT LABEL

11. The chemical names of the active ingredients on the label are identical to those on the CSF: ● yes [X] ● no [ ]

12. The appropriate physical and chemical hazards statement regarding flammability or explosive characteristics of the product are given on the label:
● yes [ ] ● no [ ] ● not applicable [X]

13. The storage and disposal instructions for the pesticide and container are in compliance with PR Notice 84-1 for household use products or PR Notice 83-3 for all other uses:
● yes [X] ● no [ ]

PRODUCT CHEMISTRY DATA (SERIES 830 Subgroup A & Subgroup B)

14. Chemical IDs/Manufacture/ Analytical Information New Guideline:830.--	Data Required Fulfilled	MRID No.
1550.(61-1)Chemical Identity(CSF)	Y	450969-02
1600.(61-2a) Beginning Materials 1620.(61-2b) Formulation Process	Y	450969-02
1670.(61-3) Discussion of Impurities	Y	450969-02
1700.(62-1) Preliminary Analysis	Y	450969-02
1750.(62-2) Certified Limits(CSF)	N	450969-02
1800.(62-3)Enforcmnt. of Anal.Method	Y	450969-01

15. Physical/Chemical Properties New Guideline No. 830.---	Data Required Fulfilled	Value or Qualitat. Descrip.	MRID No.
6303.(63-3)Physical State	Y	Liquid	450969-03
7300.(63-7)Density/Bulk Density	Y	1.092 lbs/gal	450969-03
7000.(63-12) pH	NA	6.02	450969-03
6314.(63-14)Oxid/Red Action	Y	No ox. Or red. Action	450969-03
6315.(63-15a)Flamm.-Flsh Pt.	Y	above 100.2°C	450969-03
6315.(63-15b) Flame Exten.	NA		--
6316.(63-16)Explodability	N	--	--
6317.(63-17)Storage Stability.	N	--	--
7100.(63-18)Viscosity	Y	5.13 cSt	450969-03

6319.(63-19) Miscibility	N	--	--
6320.(63-20) Corrosion Characteristics	Y	Non-corrosive as packaged, tested for about 30 days	450969-03
6321.(63-21) Dielectric Breakdown Voltage	N	---	--

Explanations: Y = The Requirements Were Fulfilled; N = The Requirements Were Not Fulfilled; NA = Not Applicable; G = Data Gap; U = Requires Upgrading; I = Incomplete or In Progress; W = Waived.

CONFIDENTIAL APPENDIX

SUBJECT: PRODUCT CHEMISTRY REVIEW OF MP [ ] EP [X]
DP BARCODE No.: D265763 REG./File Symbol No.: 11556-REA
PRODUCT NAME: Advantage Plus 9 for Cats
COMPANY: Bayer Corporation

- The CSF for the subject product, contains a nominal concentration of imidacloprid of 8.9% and of pyriproxyfen of 0.45%, not 9.10% and 0.46%, respectively, as stated on the proposed label. The registrant should resubmit the CSF and proposed label and ensure that these percentages are correct and identical.

- The subject product is not substantially similar or similar to Advantage 9, Reg. No. 11556-116, because it contains the additional a.i. pyriproxyfen and the additional inert, [redacted]

Inert ingredient information may be entitled to confidential treatment

(Front Panel)

Advantage Plus® 9

Topical Solution

Once-A-Month Topical Flea Treatment for Cats and Kittens 7 Months and Older and 9 lbs. and Under

READ THE ENTIRE LABEL BEFORE EACH USE

For the Prevention and Treatment of Flea Infestations

- Available Only Through Licensed Practicing Veterinarians
- Kills 98-100% of the Fleas on Cats Within 12 Hours
- Kills Reinfesting Fleas Within 2 Hours
- One Treatment Prevents Further Flea Infestation For Up to Four Weeks
- Kills Adult Fleas, Eggs, and Larvae
- Prevents Immature Fleas from Developing into Biting, Breeding Adults
- Provides 3-way Protection Against Fleas, Breaking Life Cycle at Egg, Larval, and Adult Stages

Active Ingredients	% By Weight
Imidacloprid; 1-[(6-Chloro-3-pyridinyl) methyl]-N-nitro-2-imidazolidinimine . .	9.10%
Pyriproxyfen; 2-[1-methyl-2-(4-phenoxyphenoxy)ethoxy] pyridine	0.46%
Inert Ingredients	90.44%
Total	100.00%

KEEP OUT OF REACH OF CHILDREN

CAUTION

See Below for First Aid and Precautionary Statements

PRECAUTIONARY STATEMENTS
HAZARDS TO HUMANS

Harmful if swallowed. Causes moderate eye irritation. Avoid contact with eyes or clothing. Wash hands thoroughly with soap and warm water after handling.

HAZARDS TO DOMESTIC ANIMALS

For external use only.
Do not use on kittens under 7 months of age.

As with any product, consult your veterinarian before using this product on debilitated, aged, pregnant or nursing animals. Individual sensitivities, while rare, may occur after using ANY pesticide product for pets. If signs persist, or become more severe, consult a veterinarian immediately. If your animal is on medication, consult your veterinarian before using this or any other product. For consumer questions call 1-800-255-6826. For medical emergencies call 1-877-258-2280.

FIRST AID

If in eyes: Hold eye open and rinse slowly and gently with water for 15-20 minutes. Remove contact lenses, if present, after the first 5 minutes, then continue rinsing eye. Call a poison control center or doctor for treatment advice.

If swallowed: Call a Poison Control Center or doctor immediately for treatment advice. Have person sip a glass of water if able to swallow. Do not induce vomiting unless told to do so by the poison control center or doctor. Do not give anything to an unconscious person.

If on skin: Wash with plenty of soap and water.

To Physician: Treat the patient symptomatically.

Four 0.4 mL Tubes

EPA Est. 11556-DEU-1
EPA Reg. No. 11556-XXX

Manufactured For

Bayer Corporation
Agriculture Division
Animal Health
Shawnee Mission, Kansas 66201 USA

Made in Germany

(Back Panel)

Advantage Plus® 9

Topical Solution
Fast
Effective
Multi-Stage Flea Control

Once-A-Month Topical Flea Treatment for Cats and Kittens 7 Months and Older and 9 lbs. and Under

- Available only through licensed practicing veterinarians
- Kills fleas within 12 hours
- Kills reinfesting fleas within 2 hours
- Prevents reinfestation for up to 4 weeks
- Convenient, easy to apply
- Kills adult fleas, eggs and larvae

Four 0.4 mL Tubes

(Inside Left Panel)

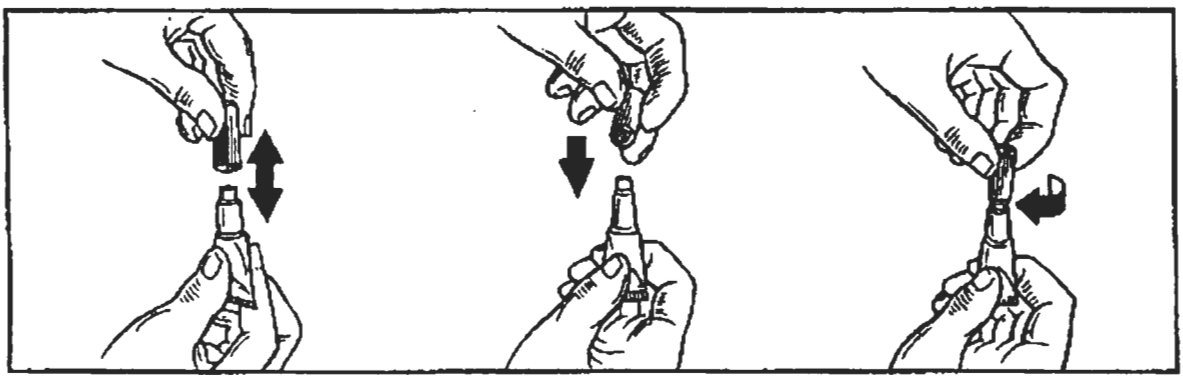
For the Prevention and Treatment of Flea Infestation on Cats and Kittens 7 Months and Older and 9 lbs and Under.

DIRECTIONS FOR USE

It is a violation of Federal Law to use this product in a manner inconsistent with its labeling.

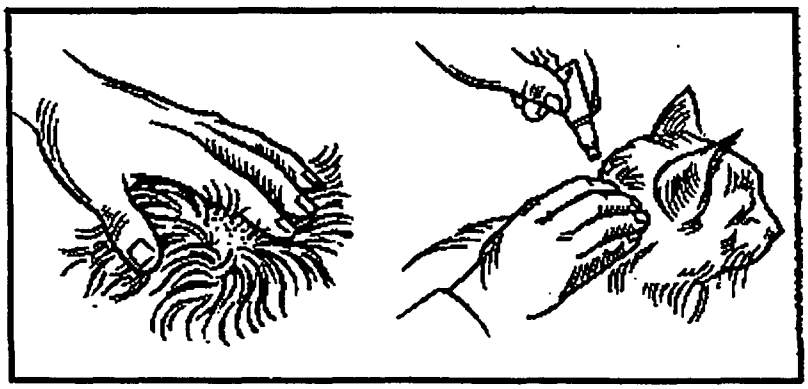
HOW TO APPLY

1. Use only on cats. Do not use on other animals.
2. Remove one applicator tube from the package.



3. Hold applicator tube in an upright position. Pull cap off tube.
4. Turn the cap around and place other end of cap back on tube.
5. Twist cap to break seal, then remove cap from tube.

6. Part the hair in the neck at the base of the skull until the skin is visible. Place the tip of the tube on the skin and squeeze the tube twice to expel the entire contents of the tube directly on the skin. Do not get this product in your pet's eyes or mouth. The product is bitter tasting and salivation may occur for a short time if the cat licks the product immediately after treatment. Treatment at the base of the skull will minimize the opportunity for the cat to lick the product.



7. Discard empty tube as described in Storage and Disposal.

(Inside Right Panel)

Advantage Plus® 9

Topical Solution

Once-a-Month topical flea treatment for cats and
kittens 7 months and older and 9 lbs. and under.

The successive feeding activity of fleas on pets frequently elicits a hypersensitivity skin disorder known as flea allergy dermatitis (FAD). Treatment of pets with Advantage Plus® rapidly kills fleas and reduces the incidence of this condition.

Advantage Plus® kills 98-100% of the existing fleas on pets within 12 hours. Reinfesting fleas are killed within 2 hours with protection against further flea infestation lasting for up to four (4) weeks. Pre-existing pupae in the environment may continue to emerge for six (6) weeks or longer depending upon the climatic conditions.

Fleas, eggs and larvae in the pet's surroundings are killed following contact with an Advantage Plus® treated pet. Advantage Plus® provides multi-stage flea control effectively breaking all flea life-cycle stages for quick and lasting control of flea populations.

Advantage Plus® kills adult fleas quickly, inhibits the development of immature flea life stages and prevents them from reaching the biting adult stage.

Advantage Plus® remains efficacious following a shampoo treatment, swimming or after exposure to rain or sunlight.

Monthly treatments are required for optimal control and prevention of fleas.

If re-treatment becomes necessary earlier than four weeks, do not re-treat more than once weekly.

STORAGE AND DISPOSAL

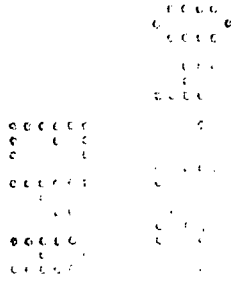
Do not contaminate water, food or feed by storage or disposal.

Storage: Store in a cool, dry place. **Pesticide Disposal**: Securely wrap original container in several layers of newspaper and discard in trash. **Container Disposal**: Do not reuse empty container. Wrap container and put in trash.

LIMITED WARRANTY AND LIMITATION OF DAMAGES

Bayer Corporation, Agriculture Division, Animal Health warrants that this material conforms to the chemical description on the label. BAYER CORPORATION MAKES NO OTHER EXPRESS OR IMPLIED WARRANTY, INCLUDING ANY OTHER EXPRESS OR IMPLIED WARRANTY OF FITNESS OR MERCHANTABILITY, and no agent of Bayer Corporation is authorized to do so except in writing with a specific reference to this warranty. Any damages arising from a breach of this warranty shall be limited to direct damages and shall not include consequential commercial damages such as loss of profits or values, etc.

Use these calendar stickers to remind you when your pet is due for its next monthly application of Advantage Plus®.



(Label on Individual Tube)

Advantage Plus®

9.10% Imidacloprid

0.46% Pyriproxyfen

0.4 mL

EPA Reg. No. 11556-XXX

CAUTION

Keep Out of Reach of Children

Read The Entire Label Before Use

BAYER

Lot No. 0000000

NFT

B

Please read instructions on reverse before completing form.

Form Approved. OMB No. 2070-0060. Approval expires 2-28-95

EPA

United States
Environmental Protection Agency
Washington, DC 20460

☑ Registration
☐ Amendment
☐ Other

OPP Identifier Number

NFT

Application for Pesticide - Section I

1. Company/Product Number	2. EPA Product Manager	3. Proposed Classification
11556-REA	Dr. Tina Levine	☑ None ☐ Restricted
4. Company/Product (Name)	**PM#**	
Advantage Plus 9 for Cats	04	

5. Name and Address of Applicant *(Include ZIP Code)*

Bayer Corporation, Animal Health, Agriculture Division
P.O. Box 390
Shawnee Mission, KS 66201

☐ *Check if this is a new address*

6. Expedited Reveiw. In accordance with FIFRA Section 3(c)(3)(b)(i), my product is similar or identical in composition and labeling to:

EPA Reg. No. _____

Product Name _____

Section - II

☐ Amendment - Explain below.

☐ Resubmission in response to Agency letter dated _____

☐ Notification - Explain below.

☐ Final printed labels in repsonse to Agency letter dated _____

☐ "Me Too" Application.

☑ Other - Explain below.

Explanation: Use additional pege(s) if necessary. (For section I and Section II.)

See Attachment

Section - III

1. Material This Product Will Be Packaged In:

Child-Resistant Packaging	Unit Packaging	Water Soluble Packaging	2. Type of Container
☐ Yes ☑ No	☐ Yes ☑ No	☐ Yes ☑ No	☐ Metal ☑ Plastic ☐ Glass ☑ Paper ☐ Other (Specify) _____
* *Certification must be submitted*	If "Yes" Unit Packaging wgt. / No. per container	If "Yes" Package wgt / No. per container	

3. Location of Net Contents Information	4. Size(s) Retail Container	5. Location of Label Directions
☑ Label ☐ Container	Four 0.4 ml tubes and Six 0.4 ml tubes	☑ On Label ☐ On Label accompanying product

6. Manner in Which Label is Affixed to Product ☐ Lithograph ☐ Paper glued ☐ Stenciled ☑ Other See Application text

Section - IV

1. Contact Point *(Complete items directly below for identification of individual to be contacted, if necessary, to process this application.)*

Name	Title	Telephone No. (Include Area Code)
F. Terry McNamara	Manager, Preclinical Development	(913) 268-2588

Certification

I certify that the statements I have made on this form and all attachments thereto are true, accurate and complete. I acknowledge that any knowlingly false or misleading statement may be punishable by fine or imprisonment or both under applicable law.

6. Date Application Received (Stamped)

2. Signature	3. Title
F. Terry McNamara	Manager, Preclinical Development
4. Typed Name	**5. Date**
F. Terry McNamara	April 7, 2000

EPA Form 8570-1 (Rev. 3-94) Previous editions are obsolete. White - EPA File Copy (original) Yellow - Applicant Copy

Please read instructions on reverse before completing form. Form Approved. OMB No. 2070-0060

EPA

United States
Environmental Protection Agency
Washington, DC 20460

☐ Registration
☐ Amendment
☐ Other

OPP Identifier Number
270787

Application for Pesticide - Section I

1. Company/Product Number	2. EPA Product Manager	3. Proposed Classification ☐ None ☐ Restricted
4. Company/Product (Name)	PM#	

5. Name and Address of Applicant *(Include ZIP Code)*

☐ *Check if this is a new address*

6. **Expedited Review.** In accordance with FIFRA Section 3(c)(3)(b)(i), my product is similar or identical in composition and labeling to:

EPA Reg. No. _____

Product Name _____

Section - II

☐ Amendment - Explain below.
☐ Resubmission in response to Agency letter dated _____
☐ Notification - Explain below.
☐ Final printed labels in response to Agency letter dated _____
☐ "Me Too" Application.
☐ Other - Explain below.

Explanation: Use additional page(s) if necessary. (For section I and Section II.)

Section - III

1. Material This Product Will Be Packaged In:

Child-Resistant Packaging	Unit Packaging	Water Soluble Packaging	2. Type of Container
☐ Yes* ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Metal ☐ Plastic ☐ Glass ☐ Paper ☐ Other (Specify) _____
Certification must be submitted	If "Yes" Unit Packaging wgt. / No. per container	If "Yes" Package wgt / No. per container	

3. Location of Net Contents Information	4. Size(s) Retail Container	5. Location of Label Directions
☐ Label ☐ Container		☐ On Label ☐ On Labeling accompanying product

6. Manner in Which Label is Affixed to Product ☐ Lithograph ☐ Paper glued ☐ Stenciled ☐ Other _____

Section - IV

1. Contact Point *(Complete items directly below for identification of individual to be contacted, if necessary, to process this application.)*

Name	Title	Telephone No. (Include Area Code)

Certification

I certify that the statements I have made on this form and all attachments thereto are true, accurate and complete. I acknowledge that any knowingly false or misleading statement may be punishable by fine or imprisonment or both under applicable law.

6. Date Application Received (Stamped)

2. Signature	3. Title
4. Typed Name	5. Date

EPA Form 8570-1 (Rev. 8-94) Previous editions are obsolete. White - EPA File Copy (original) Yellow - Applicant Copy

PAPERWORK REDUCTION ACT NOTICE and INSTRUCTIONS

PAPERWORK REDUCTION ACT NOTICE: Public reporting burden for this collection of information is estimated to average 0.85 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding the burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Chief, Information Policy Branch, (2136), U.S. Environmental Protection Agency, 401 M Street, SW, Washington, DC 20460.

INSTRUCTIONS: This form is to be used for all applications for new registration, end use reregistration, amendment, resubmission, to applications for notifications, final printed labeling, reregistration, etc. In order to process an application for a new registration submitted on this form, the following material must accompany the application:

1. Certification with Respect to Citation of Data (EPA Form 8570-29). [If not exempted by 40 CFR 152.81 (b) (4)];
2. Confidential Statement of Formula (EPA Form 8570-4);
3. Formulator's Exemption Statement (EPA Form 8570-27);
4. Five copies of draft labeling;
5. Three copies of any data submitted;
6. Authorization letter where applicable;
7. Matrices where applicable.

Submission of Labeling - Labeling should first be submitted in the form of draft labels with all applications for new registration. Such draft labels may be in the form of typed label text on 8.5 x 11 inch paper for submission or a mockup of the proposed label. If prepared for mockup, it should be constructed in a way as to facilitate storage in an 8.5 x 11 inch file. Mockup labels significantly smaller than 8.5 x 11 inches should be mounted on 8.5 x 11 inch paper for submission.
Submission of Data - Data submitted in support of this application must be submitted in accordance with PR Notice 86-5.

SPECIFIC INSTRUCTIONS: Please read the instructions listed below before completing this application. First determine the type of registration action, listed in Block A, for which you are submitting this application. For applications submitted in connection with New Registration actions, Sections I, III, and IV must be completed by the applicant. For applications submitted in connection with amended reregistration actions, resubmissions, notifications, reregistrations, etc., Sections I, II, and IV must be completed by the applicant.
Block A - Check the appropriate action for which you are submitting this form.

SECTION I - This section must be completed, as applicable, for all registration actions.

1. Company/Product Number - Insert your Company Number, if one has been assigned by EPA. This number may have been assigned to you as a basic registrant, a distributor, or as an establishment. If your product is registered, insert the Product Number.
2. EPA Product Manager - If known, fill in the name and PM number of the EPA Product Manager.
3. Proposed Classification - Specify the proposed classification of this product.
4. Product Name - Enter the complete product name of this pesticide as it will appear on the label. The name must be specific to this product only. Duplication of names is not permitted among products of the same company. Do not include any brand name or company line designations.
5. Name and Address of Applicant - The name of the firm or person and address shown in your application is the person or firm to whom the registration will be issued. If you are acting in behalf of another party, you must submit authorization from that party to act for them in registration matters. An applicant not residing in the United States must have an authorized agent residing in the United States to act for them in all registration matters. The name and complete mailing address of such an agent must accompany this application.
6. Expedited Review - FIFRA section 3 (c) 3 (B) provides for expedited raview of applications for registration, or amendments to existing registrations, that are similar or identical to other pesticide products that are currently registered with the EPA. In order for your application to be eligible for expedited review, you must provide us with the EPA Registration Number and product name of the product you believe is similar to or identical your product. The product must be similar or identical in both formulation and labeled uses.

SECTION II - This section must be completed for all applications submitted to amend the registration only of a currently registered product (Amendment), for a resubmission in response to an Agency letter, for notifications to the Agency, for the submission of final printed labeling, for reregistration and for any other action that pertains to a specific EPA-registered product. This section is not to be used for a new application for registration.

1. Subject of submission - Check the applicable block and provide the Agency letter date if appropriate. Provide a brief explanation of the purpose(s) for the submission, such as "the addition of a site, pest or crop (specify)"; "amend the Confidential Statement of Formula by..."; "reregistration submission"; "general label revision of use directions." Attach a separate page if additional space is needed.

SECTION III (Packaging and Container Information) - This Section must be completed for all applications submitted in connection with new registration or applicable amendments.

1. **Type of Packaging** - Check the appropriate block if your product will be packaged in the indicated packaging types. Indicate the size of the individual packets and number per retail conteiner.
2. **Type of Retail Container** - Indicate type of container in which product will be marketed.
3. **Location of Net Contents** - Indicate the location of the net contents information for your product.
4. **Size(s) of Retail Container** - Specify the net contents of all retail containers for your product.
5. **Location of Use Directions** - Indicate the location of the use directions for your product.
6. **Manner in which label is affixed to product** - Indicated the method product label is attached to retail container.

SECTION IV (Contact Point) - This Section must be completed for all applications for Registration actions, i.e., new products registration, resubmission, "me-too," reregistration, etc.

1-5. Self-explanatory.
6. EPA Use Only.

Please read instructions on reverse before completing form. Form Approved. OMB No. 2070-0060

EPA

United States
Environmental Protection Agency
Washington, DC 20460

☐ Registration
☐ Amendment
☐ Other

OPP Identifier Number
2270/877

Application for Pesticide - Section I

1. Company/Product Number	2. EPA Product Manager	3. Proposed Classification ☐ None ☐ Restricted
4. Company/Product (Name)	PM#	
5. Name and Address of Applicant *(Include ZIP Code)* ☐ *Check if this is a new address*	6. **Expedited Review.** In accordance with FIFRA Section 3(c)(3)(b)(i), my product is similar or identical in composition and labeling to: EPA Reg. No. _____ Product Name _____	

Section - II

☐ Amendment - Explain below.
☐ Resubmission in response to Agency letter dated _____
☐ Notification - Explain below.
☐ Final printed labels in response to Agency letter dated _____
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☐ Other - Explain below.

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Certification must be submitted	If "Yes" Unit Packaging wgt. / No. per container	If "Yes" Package wgt / No. per container	

3. Location of Net Contents Information	4. Size(s) Retail Container	5. Location of Label Directions
☐ Label ☐ Container		☐ On Label ☐ On Labeling accompanying product

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3. Proposed Classification - Specify the proposed classification of this product.
4. Product Name - Enter the complete product name of this pesticide as it will appear on the label. The name must be specific to this product only. Duplication of names is not permitted among products of the same company. Do not include any brand name or company line designations.
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2. Type of Retail Container - Indicate type of container in which product will be marketed.
3. Location of Net Contents - Indicate the location of the net contents information for your product.
4. Size(s) of Retail Container - Specify the net contents of all retail containers for your product.
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1-5. Self-explanatory.
6. EPA Use Only.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

04/13/2000

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

Bayer Corporation, Animal Health, Agriculture Division
P.O. Box 390
Shawnee Mission, KS 66201

PRODUCT NAME: Advantage Plus 9 for Cats
COMPANY NAME: Bayer Corporation, Animal Health, Agriculture Division
OPP IDENTIFICATION NUMBER: 270787
EPA FILE SYMBOL: 11556-REA
EPA RECEIPT DATE: 04/12/00

SUBJECT: RECEIPT OF APPLICATION FOR A NEW REGISTRATION

DEAR REGISTRANT:

The Office of Pesticides Programs has received your application for a new registration and it has passed an administrative screen for completeness.

Please note that this is only a notification of receipt of your application. This is only the first step in the application process, and does NOT constitute approval.

If you have any questions, please contact the Insecticide /Rodenticide Branch, at (703)-305-5404.

Sincerely,

Front End Processing Staff
Information Resources & Services Division
Information Services Branch

Bayer

April 7, 2000

Agriculture Division

Crop Protection Products

Bayer Corporation
8400 Hawthorn Road
P.O. Box 4913
Kansas City, MO 64120-0013
Phone: 816 242-2000

Ms. Dani Daniel
Registration Division (H7505C)
U.S. Environmental Protection Agency
Ariel Rios Building
1200 Pennsylvania Avenue, N.W.
Washington, D.C. 20460

Subject: **Letter of Authorization; BAYER Animal Health ADVANTAGE Plus® Applications for Registration, Imidacloprid**

Dear Ms. Daniel,

BAYER Corporation, Agriculture Division, hereby authorizes the Agency to refer to any research and/or test data on our active ingredient imidacloprid (the active ingredient in ADMIRE® and PROVADO®) in support of the applications for registration of ADVANTAGE Plus® 10, ADVANTAGE Plus® 20, ADVANTAGE Plus® 55, ADVANTAGE Plus® 100, ADVANTAGE Plus® 9, ADVANTAGE Plus® 18, submitted by BAYER Animal Health, 12707 W. 63rd St., Shawnee Mission, KS, 66216-1846.

Furthermore, the Agriculture Division of BAYER Corporation has three business groups; Crop Protection, Specialty, and Animal Health. All three business groups seek product registrations for products containing the active ingredient imidacloprid. Any confidential business information released by the Agency in data evaluation records or other documents for company number 3125 (Crop Protection and Specialty Groups) can be disclosed without restriction to the Animal Health Group, company number 11556. In addition, the Agency is authorized to refer to any research and test data submitted under company number 3125 in support of applications for registration from BAYER Animal Health, company number 11556.

As always, if you have any questions, feel free to call me at (816) 242-2838.

Sincerely,

BAYER Corporation, Agriculture Division

James L. Kunstman
Manager, Product Registrations

ATTACHMENT
FOR
APPLICATION FOR PESTICIDE REGISTRATION

Advantage Plus® 9 for Cats

With this application form and the enclosed documents, Bayer Corporation requests the registration of Advantage Plus® 9 for Cats, a new insecticide product.

Briefly, this product will consist of a blister package constructed of cardboard, plastic and foil containing individual plastic tubes each containing 0.4 ml of the liquid insecticide. There will be two package sizes – a 4-tube package and a 6-tube package. The outer blister package will contain all of the draft labeling text, dated 4/7/2000, which is enclosed (5 copies each). The individual plastic tubes inside the blisters will contain only the draft labeling indicated on page 8 of the label text, again dated 4/7/2000, which is enclosed (5 copies each). Please note, because the tubes are very small in size, we are proposing that only the product name, the active ingredients, the amounts of the active ingredients and the EPA Reg. No. be printed onto each tube (again, the overall blister package will contain complete labeling). Also note, this packaging and labeling scheme is identical to that used by Bayer's currently registered product, Advantage® 9 for Cats (EPA Reg. No. 11556-116).

PRODUCT CHEMISTRY

The insecticide formulation is a liquid solution of imidacloprid (9.1% w/w) and pyriproxyfen (0.46% w/w) in inert ingredients which are on EPA's list of acceptable inert ingredients for use in pesticides. Two (2) copies of the Confidential Statement of Formula (CSF) for this product are enclosed. The source of the active ingredients for this product are NTN 33893 Technical, EPA Reg. No. 3125-414, and [redacted]. The product chemistry data to support the registration of this new formulation are in the following Bayer Reports:

Bayer Report No. 75133 entitled "Product Chemistry of (10% w/v, 9.1% w/w) Imidacloprid + (0.5% w/v, 0.46% w/w) Pyriproxyfen Topical Solution – OPPTS 830 – Group A: Product Identity, Composition, and Analysis",

Bayer Report No. 75132 entitled "Product Chemistry of (10% w/v, 9.1% w/w) Imidacloprid + (0.5% w/v, 0.46% w/w) Pyriproxyfen Water Topical Solution, OPPTS 830 Group B – Physical/Chemical Properties" and,

111

Product ingredient source information may be entitled to confidential treatment

Bayer Report No. 75130 entitled "Validation of Bayer Animal Health Test Method TMC-14.02 for the Determination of Imidacloprid and Pyriproxyfen Topical Solution Formulation by HPLC."

Three (3) copies of each of these reports accompany this application. Although the report titles do not use the "Advantage Plus" trade name, the formulation described and tested is Advantage Plus® 9 for Cats.

Also, these three product chemistry reports support the registration of the five other Advantage Plus® products (Advantage Plus® 18 for Cats, and Advantage Plus® 10, Advantage Plus® 20, Advantage Plus® 55 and Advantage Plus® 100 for dogs) whose applications are accompanying this application.

TOXICOLOGY

Also enclosed with this application are three (3) copies of the following six reports describing the results of Guideline 870.1100 through 870.2600 acute toxicology testing:

EPA Guideline Number	Bayer Report Number	Bayer Report Title
870.1100	75195	Acute Oral Toxicity Study with Imidacloprid (9.1%) /Pyriproxyfen (0.9%) Spot On in Rats
870.1200	75196	Acute Dermal Toxicity Study with Imidacloprid (9.1%)/Pyriproxyfen (0.9%) Spot On in Rats
870.1300	75197	Acute 4-Hour Inhalation Toxicity Study with Imidacloprid (9.1%)/Pyriproxyfen (0.9%) Spot On in Rats
870.2400	75199	Primary Eye Irritation Study in Rabbits with Imidacloprid (9.1%)/Pyriproxyfen (0.9%)/5.0% Water Spot On
870.2500	75200	Primary Dermal Irritation Study in Rabbits with Imidacloprid (9.1%)/Pyriproxyfen (0.9%) Spot On
870.2600	75201	Dermal Sensitization Study in Guinea Pigs – Closed Patch Technique with Imidacloprid (9.1%)/Pyriproxyfen (0.9%) Spot On

Please note, the study titles refer to test materials with a slightly different formulation than that which is proposed for registration. The formulation proposed for registration contains 9.1% imidacloprid, 0.46% pyriproxyfen, and [redacted] and the other inert ingredients identified on the enclosed Confidential Statement of Formula. The formulation used for five of the acute toxicity studies contained 9.1% imidacloprid and a higher pyriproxyfen concentration (0.9%) [redacted] The formulation used for the primary eye irritation study (Bayer Report No. 75199) contained 9.1% imidacloprid, 0.9% pyriproxyfen, and [redacted] as documented in the Confidential Appendix to Report No. 75199). These studies are being submitted in support of the registration for the formulation with 0.46% pyriproxyfen. As per EPA's November 2, 1999 meeting with Bayer, the Agency's technical reviewers (Byron Backus and John Redden) confirmed that EPA would accept these studies since the formulation tested represents a "worst case" compared to the current formulation proposed for registration.

Also, the above cited six toxicology reports support the registration of the five other Advantage Plus® products whose applications are accompanying this application.

The results of the toxicology studies demonstrate that the appropriate signal word is "CAUTION" for all six Advantage Plus® products. The toxicity categories based on the study results are summarized below.

Study Type	Bayer Report Number	Toxicity Category
Acute Oral	75195	III
Acute Dermal	75196	IV
Acute Inhalation	75197	IV
Primary Eye Irritation	75199	III
Primary Dermal Irritation	75200	IV
Dermal Sensitization	75201	Negative

To address the Guideline 870.7200 (86-1) Domestic Animal Safety requirement for Advantage Plus® 9 for Cats (and also Advantage Plus® 18 for Cats), three (3) copies of Bayer Report No. 75122 entitled "Evaluation of the General Safety of 9.1% Imidacloprid with 0.9% Pyriproxyfen Spot-on Formulation in the Target Species, Adult Cats," are enclosed with this application.

Also, the above cited domestic animal safety study supports the registration of the other Advantage Plus® product for cats - Advantage Plus® 18 for Cats - whose application accompanies this application.

EFFICACY

To support the claim of flea control for the Advantage Plus® 9 (and 18) product(s) on cats, Bayer is citing studies previously submitted to, reviewed by, and accepted by the Agency for Bayer's currently registered Advantage® 9 for Cats (EPA Reg. No. 11556-116) and Advantage 18 for Cats (EPA Reg. No. 11556-118) products. Specifically, these reports are:

> EPA MRID 43679503 entitled "Efficacy Evaluation of Bay t 7391 (Imidacloprid) 10% Solution Applied Dermally for Control of Fleas on Cats" (Bayer Report No. 74571) and,
>
> EPA MRID 43679504 entitled "Efficacy Evaluation of Bay t 7391 (Imidacloprid) 10% Solution Applied Dermally for Control of Fleas on Cats" (Bayer Report No. 74581).
>
> EPA MRID 43679609 entitled "Efficacy Evaluation of Bay t 7391 (Imidacloprid) 10% Solution Applied Dermally for Control of Fleas on Dogs" (Bayer Report No. 74572) and,
>
> EPA MRID 43679610 entitled "Efficacy Confirmation of Bay t 7391 (Imidacloprid) 10% Solution Applied Dermally for Control of Fleas on Dogs" (Bayer Report No. 74541).

The above referenced studies support the once-per-month use of imidacloprid (Advantage®) to control fleas and, therefore, the once-per-month use of imidacloprid in Advantage Plus® to control fleas.

The currently accepted labels for Advantage® 9 and 18 for Cats and the draft proposed labels for Advantage Plus® 9 and 18 for Cats have a claim for water resistance of the product, larvicidal efficacy, and a 12-hour "speed of kill" claim. These claims are supported by Bayer studies previously submitted to, reviewed by, and accepted by the Agency for Bayer's currently registered products Advantage® 9 for Cats (EPA Reg. No. 11556-116) and Advantage 18 for Cats (EPA Reg. No. 11556-118). Specifically, these reports are:

> EPA MRID 44256903 entitled "Evaluation of the Effects of Shampooing or Water Immersion on the Initial and Residual Efficacy of Advantage® for Flea Control on Dogs" (Bayer Report No. 74792),

EPA MRID 44256902 entitled "Imidacloprid Topical Formulation: Larvicidal Effect Against *Ctenocephalides felis* in the Surroundings of Treated Dogs" (Bayer Report No. 74828) and,

EPA MRID 44256901 entitled "Comparative Evaluation of How Quickly Advantage® and Frontline™ (fipronil) Top Spot Kill Fleas on Dogs" (Bayer Report No. 74800).

Whereas Advantage® was efficacious against larval and adult fleas, the new Advantage Plus® product is effective against flea larvae, adult fleas, and flea eggs. The active ingredient, pyriproxyfen, is currently registered in at least 92 products for many different uses. Among these registrations, there are at least 13 currently registered pyriproxyfen flea products which range in active ingredient concentration from 0.125 to 5.3 percent. The concentration of pyriproxyfen in Advantage Plus® (0.46%) falls within the range of concentrations of the currently registered products.

Bayer is citing four efficacy studies for pyriproxyfen. [redacted]

"Evaluation of Two Concentrations of Nylar (Pyriproxyfen) in a Dip and Shampoo Formulation Against the Hatch of Flea Eggs Collected from Treated Cats" (MGK Report No. OT018-94),

"Flea Eggs: Target of the New IGR On-Animal Treatments" (MGK Report No. OT016-93),

"Final Report on Comparison of Isopropyl Alcohol Dilutions of Pyriproxyfen and Fenoxycarb on Hatchability of Flea Eggs" (MGK Report No. OT006-96) and,

"Final Report on the Physiological Effects of Pyriproxyfen on Adults and Eggs of the Cat Flea, *Ctenocephalides felis* (MGK Report No. OT023-93).

The results of these studies support the once-a-month application rate for Advantage Plus® since the efficacious concentration of pyriproxyfen used in the studies was lower than the concentration in the formulation proposed for registration. In addition, the lower concentration of pyriproxyfen was shown to be effective for a period greater than one month.

These efficacy study reports also support the registration of the other Advantage Plus® product for cats - Advantage Plus® 18 for Cats - whose application accompanies this application.

DATA COMPENSATION

An appropriate data matrix listing all of the data necessary to support the registration of Advantage Plus® 9 (and also the other Advantage Plus® product for cats) is enclosed with this application. Please note, the enclosed data matrix cites only those data necessary for this registration. This registration application is for a product used only on cats (classified as an indoor, non-food use); the data matrix does not cite any imidacloprid environmental fate, ecological effects nor residue chemistry data because these data are not necessary for this proposed registration.

Generic Data

With regard to imidacloprid, the Crop Protection group of Bayer Corporation's Agriculture Division is the basic registrant of imidacloprid therefore, the Animal Health group cannot claim Formulator's Exemption for the generic data requirements. Accordingly, enclosed is a copy of Letter of Authorization from the other group (EPA Company No. 3125) of the Agriculture Division authorizing the use of the generic imidacloprid data by the Animal Health group (EPA Company No. 11556) of the Agriculture Division. These generic data are cited in the enclosed data matrix.

With regard to pyriproxyfen, a completed Formulator's Exemption form (EPA Form 8570-27) is enclosed with this application for Bayer to address compensation of pyriproxyfen generic data. Also, enclosed with this application is a Letter of Authorization from Sumitomo Chemical Company Ltd.

Product Specific Data

All of the data necessary to support the registration of Advantage Plus® 9 are data previously submitted by Bayer's Animal Health group (EPA Company No. 11556) or are enclosed with this application or were submitted by the [redacted] Enclosed with this application is a Letter of Authorization from MGK. All of these data are cited in the enclosed data matrix.

As demonstrated in the enclosed, completed Certification With Respect to Citation of Data (EPA Form 8570-29), we are choosing the Selective Method of Support for pyriproxyfen efficacy data. Again, a Letter of Authorization from MGK to cite these data is enclosed.

CHILD RESISTANT PACKAGING

Certification that the packaging for Advantage Plus® 9 meets the child-resistant packaging standards in 40 CFR 157.32 is not necessary because Advantage Plus® 9 does not meet any of the toxicity criterion listed in 40 CFR 157.22 (a) for products requiring child resistant packaging.

Form Approved. OMB No. 2070-0060. Approval Expires 5-31-98.

United States
Environmental Protection Agency
Washington, DC 20460

Formulator's Exemption Statement
(40 CFR 152.85)

Applicant's Name and Address	EPA File Symbol/Registration Number
Bayer Corporation Animal Health, Agriculture Division P. O. Box 390 Shawnee Mission, KS 66201	11556-~~XXX~~ REA
	Product Name Advantage Plus 9 for Cats
	Date of Confidential Statement of Formula *(EPA Form 8570-4)* April 7, 2000

As an authorized representative of the applicant for registration of the product identified above, I certify that:

(1) This product contains the following active ingredient(s):

Pyriproxyfen
Imidacloprid (not citing Formulator's Exemption for this active ingredient)

(2) Of these, each active ingredient listed in paragraph (4) is present solely as the result of the use of that active ingredient in the manufacturing, formulation or repackaging another product which contains that active ingredient which is registered under FIFRA Section 3, is purchased by us from another producer, and is labeled for at least each use for which my product is proposed to be labeled.

(3) Indicate by checking (A) or (B) below which paragraph applies:

☑ **(A) An accurate Confidential Statement of Formula** *(EPA FORM 8570-4)* **for the above identified product is attached to this statement. That formula statement indicates, by company name, registration number, and product name, the source of the active ingredient(s) listed in paragraph (1).**

OR

☐ **(B) The Confidential Statement of Formula (CSF) (EPA Form 8570-4) referenced above and on file with the EPA is complete, current, and accurate and contains the information required on the current CSF.**

(4) The following active ingredients in this product qualify for the formulator's exemption.

Source

Active Ingredient	Product Name	Registration Number
[redacted]	[redacted]	[redacted]

Signature	Name and Title	Date
F. T. McNamara	F. T. McNamara Mgr, Preclinical Dev.	April 7, 2000

EPA Form 8570-27 (Rev. 8-95)

White - EPA copy
Yellow - Applicant copy

★ U.S. GPO: 1995-386-820/20413

Product ingredient source information may be entitled to confidential treatment

Form Approved OMB No. 2070-0060

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
401 M Street, S.W.
WASHINGTON, D.C. 20460

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Do not send the completed form to this address.

Certification with Respect to Citation of Data

Applicant's/Registrant's Name, Address, and Telephone Number	EPA Registration Number/File Symbol
Bayer Corporation, Animal Health, Agriculture Division P.O. Box 390 Shawnee Mission, KS 66201	11556-~~xx~~ REA
Active Ingredient(s) and/or representative test compound(s) Pyriproxifen; Imidacloprid	Date April 7, 2000
General Use Pattern(s) (list all those claimed for this product using 40 CFR Part 158) Indoor, Non-food	Product Name ADVANTAGE PLUS 9 for Cats

NOTE: If your product is a 100% repackaging of another purchased EPA-registered product labeled for all the same uses on your label, you do not need to submit this form. You must submit the Formulator's Exemption Statement (EPA Form 8570-27).

☐ I am responding to a Data-Call-In Notice, and have included with this form a list of companies sent offers of compensation (the Data Matrix form should be used for this purpose).

SECTION I: METHOD OF DATA SUPPORT (Check one method only)

☐ I am using the cite-all method of support, and have included with this form a list of companies sent offers of compensation (the Data Matrix form should be used for this purpose).

☑ I am using the selective method of support (or cite-all option under the selective method), and have included with this form a completed list of data requirements (the Data Matrix form must be used).

SECTION II: GENERAL OFFER TO PAY

[Required if using the cite-all method or when using the cite-all option under the selective method to satisfy one or more data requirements]

☐ I hereby offer and agree to pay compensation, to other persons, with regard to the approval of this application, to the extent required by FIFRA.

SECTION III: CERTIFICATION

I certify that this application for registration, this form for reregistration, or this Data-Call-In response is supported by all data submitted or cited in the application for registration, the form for reregistration, or the Data-Call-In response. In addition, if the cite-all option or cite-all option under the selective method is indicated in Section I, this application is supported by all data in the Agency's files that (1) concern the properties or effects of this product or an identical or substantially similar product, or one or more of the ingredients in this product; and (2) is a type of data that would be required to be submitted under the data requirements in effect on the date of approval of this application if the application sought the initial registration of a product of identical or similar composition and uses .

I certify that for each exclusive use study cited in support of this registration or reregistration, that I am the original data submitter or that I have obtained the written permission of the original data submitter to cite that study.

I certify that for each study cited in support of this registration or reregistration that is not an exclusive use study, either: (a) I am the original data submitter; (b) I have obtained the permission of the original data submitter to use the study in support of this application; (c) all periods of eligibility for compensation have expired for the study; (d) the study is in the public literature; or (e) I have notified in writing the company that submitted the study and have offered (I) to pay compensation to the extent required by sections 3(c)(1)(F) and/or 3(c)(2)(B) of FIFRA; and (ii) to commence negotiations to determine the amount and terms of compensation, if any, to be paid for the use of the study.

I certify that in all instances where an offer of compensation is required, copies of all offers to pay compensation and evidence of their delivery in accordance with sections 3(c)(1)(F) and/or 3(c)(2)(B) of FIFRA are available and will be submitted to the Agency upon request. Should I fail to produce such evidence to the Agency upon request, I understand that the Agency may initiate action to deny, cancel or suspend the registration of my product in conformity with FIFRA.

I certify that the statements I have made on this form and all attachments to it are true, accurate, and complete. I acknowledge that any knowingly false or misleading statement may be punishable by fine or imprisonment or both under applicable law.

Signature	Date	Typed or Printed Name and Title
F. Terry McNamara	April 7, 2000	F. Terry McNamara Mgr, Preclinical Development

EPA Form 8570-34 (9-97) Electronic and Paper versions available. Submit only Paper version.

MGK®
McLAUGHLIN GORMLEY KING COMPANY
8810 Tenth Avenue North • Minneapolis, Minnesota 55427-4372 U.S.A.

April 3, 2000

Mr. Marion Johnson (PM 10)
Office of Pesticide Programs (H7505C)
U.S. ENVIRONMENTAL PROTECTION AGENCY
Ariel Rios Building
1200 Pennsylvania Avenue, N.W.
Washington DC 20460

Subject: Bayer Animal Health
9009 W. 67th Street, Bldg. 1
Merriam, KS 66202

Dear Mr. Johnson:

This letter serves as authorization, in accordance with our agreement with the registrant, to refer to the following data submitted by McLaughlin Gormley King Company to EPA for the subject company's registration.

MGK Efficacy Data: Submitted to EPA Reg. No. 1021-1619 on March 30, 2000

Registrant's Product: Advantage Plus® 9
EPA Reg. No.: 11556-

Although this is authorization to rely on MGK data for the subject company's subject registration, absolutely no data of a confidential nature is to be disclosed to them.

Sincerely,

McLAUGHLIN GORMLEY KING COMPANY

Julie B. Schlekau
Registration Specialist

Product ingredient source information may be entitled to confidential treatment

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
401 M Street, S.W.
WASHINGTON, D.C. 20460 Form

Approved OMB No. 2070-0060

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DATA MATRIX

Date: April 7, 2000	**EPA Reg No./File Symbol:** 11556-~~REA~~ 11556-XXX	Page 1 of 10
Bayer Corporation - Agriculture Division, Animal Health P.O. Box 390 Shawnee Mission, KS 66201-0390	**Product:** Advantage Plus® 9 for Cats Advantage Plus® 18 for Cats	**Ingredient:** Imidacloprid, CAS = 138261-41-3 Pyriproxyfen, CAS = 95737-68-1

Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note: Report Number	Description
Product Chemistry, Section 158.240						
61-1	Chemical identity	42055302	3125	PER	BR 1759 (TGAI)	
		43306001	3125	PER	BR 1879 (TGAI)	
		42256302	3125	PER	BR 1766 (Formulation)	
61-2	Statement of Composition	42055302	3125	PER	BR 1759 (TGAI)	
		43306001	3125	PER	BR 1879 (TGAI)	
		42270801	3125	PER	BR 1785 (TGAI)	
		42256302	3125	PER	BR 1766 (Formulation)	
61-3	Formation of impurities	42055302	3125	PER	BR 1759 (TGAI)	
		42256302	3125	PER	BR 1766 (Formulation)	
62-1	Preliminary analysis	42055303	3125	PER	BR 1760 (TGAI)	
		43306002	3125	PER	BR 1880 (TGAI)	
		42270802	3125	PER	BR 1786 (TGAI)	
		42256302	3125	PER	BR 1766 (Formulation)	
62-2	Certification of limits	42055303	3125	PER	BR 1760 (TGAI)	
		43306002	3125	PER	BR 1880 (TGAI)	
		42256302	3125	PER	BR 1766 (Formulation)	
62-3	Analytical method	42055303	3125	PER	BR 1760 (TGAI)	
		43213001	3125	PER	BR 1874 (TGAI)	
		43306002	3125	PER	BR 1880 (TGAI)	
		42256302	3125	PER	BR 1766 (Formulation)	
			11556	OWN	Report No. 75130	Submitted with application for Advantage Plus® 9 for Cats

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DATA MATRIX

Date: April 7, 2000	**EPA Reg No./File Symbol:** 11556-~~XXX~~ EA, 11556-XXX	Page 2 of 10
Bayer Corporation - Agriculture Division, Animal Health P.O. Box 390 Shawnee Mission, KS 66201-0390	**Product:** Advantage Plus® 9 for Cats Advantage Plus® 18 for Cats	**Ingredient:** Imidacloprid, CAS = 138261-41-3 Pyriproxyfen, CAS = 95737-68-1

Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note / Report Number	Description
63-1	Chemical and Physical Properties	42055304	3125	PER	BR 1761 (TGAI)	
		42256302	3125	PER	BR 1766 (Formulation)	
63-2	Appearance	42055304	3125	PER	BR 1761 (TGAI)	
		42256302	3125	PER	BR 1766 (Formulation)	
63-3	Physical state	42055304	3125	PER	BR 1761 (TGAI)	
		42256302	3125	PER	BR 1766 (Formulation)	
63-4	Odor	42055304	3125	PER	BR 1761 (TGAI)	
		42256302	3125	PER	BR 1766 (Formulation)	
63-5	Melting point	42055304	3125	PER	BR 1761 (TGAI)	
63-6	Boiling point	42055304	3125	PER	BR 1761(TGAI)	
63-7	Density	42055304	3125	PER	BR 1761 (TGAI)	
		43356302	3125	PER	BR 1761 (Formulation)	
63-8	Solubility	42055304	3125	PER	BR 1761 (TGAI)	
63-9	Vapor pressure	42055304	3125	PER	BR 1761 (TGAI)	
63-10	Dissociation constant					N.A. - Doesnot dissociate
63-11	Octanol / water partition	42055304	3125	PER	BR 1761 (TGAI)	
63-12	pH	42055304	3125	PER	BR 1761 (TGAI)	
		42256302	3125	PER	BR 1766 (Formulation)	
63-13	Stability	42055304	3125	PER	BR 1761 (TGAI)	
63-14	Oxidizing / reducing action		3125	PER		N.A. - No oxidative or reductive characteristics
63-15	Flammability	42055304	3125	PER	BR 1761 (TGAI)	
63-16	Explodability	42055304	3125	PER	BR 1761 (TGAI)	

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DATA MATRIX

Date: April 7, 2000	**EPA Reg No./File Symbol:** 11556-~~XXX~~ REA, 11556-XXX	Page 3 of 10
Bayer Corporation - Agriculture Division, Animal Health P.O. Box 390 Shawnee Mission, KS 66201-0390	**Product:** Advantage Plus® 9 for Cats Advantage Plus® 18 for Cats	**Ingredient:** Imidacloprid, CAS = 138261-41-3 Pyriproxyfen, CAS = 95737-68-1

Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note: Report Number	Note: Description
		42055304	3125	PER	BR 1761 (TGAI)	
63-17	Storage stability	42256302	3125	PER	BR 1766 (Formulation)	
63-18	Viscosity		3125	PER		N.A. - Solid
63-19	Miscibility		3125	PER		N.A. - Solid
		42055304	3125	PER	BR 1761 (TGAI)	
63-20	Corrosion characteristics	42256302	3125	PER	BR 1766 (Formulation)	
63-21	Dielectric breakdown volt					N.A.- Solid
64-1	Submittal of samples				Samples available upon request	
830-Group A	Product Chemistry: Identity, Composition, Analysis		11556	OWN	Report No. 75133	Submitted with application for Advantage Plus® 9 for Cats
830-Group B	Product Chemistry: Physical/Chemical Properties		11556	OWN	Report No. 75132	Submitted with application for Advantage Plus® 9 for Cats
Wildlife and Aquatic Organisms, Section 158.490						
71-1	Acute avian oral - quail/duck					N.A.
71-2(a)	Avian dietary - quail					N.A.
71-2(b)	Avian dietary - duck					N.A.
71-3	Wild mammal toxicity					N.A.
71-4(a)	Avian reproduction - quail					N.A.
71-4(b)	Avian reproduction – duck					N.A.
71-5	Simulated or actual field study					N.A.
72-1(a)	Fish toxicity - bluegill					N.A.
72-1(b)	Fish toxicity bluegill - tep					N.A.

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DATA MATRIX

Date: April 7, 2000	**EPA Reg No./File Symbol:** 11556-[redacted], 11556-XXX RFA	Page 4 of 10
Bayer Corporation - Agriculture Division, Animal Health P.O. Box 390 Shawnee Mission, KS 66201-0390	**Product:** Advantage Plus® 9 for Cats Advantage Plus® 18 for Cats	**Ingredient:** Imidacloprid, CAS = 138261-41-3 Pyriproxyfen, CAS = 95737-68-1

Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note / Report Number	Description
72-2(a)	Invertebrate toxicity - Daphnia					N.A.
72-2(b)	Invertebrate toxicity - Amphipods					N.A.
72-2(c)	Acute aquatic invertebrate toxicity - Chironomids					N.A.
72-3(a)	Estuarine / marine toxicity - fish					N.A.
72-3(b)	Estuarine / marine toxicity - mollusk					N.A.
72-3(c)	Estuarine/marine toxicity - shrimp					N.A.
72-4(a)	Early life stage - fish					N.A.
72-4(b)	Life cycle invertebrate					N.A.
72-7	Simulated or actual field study					N.A.
None	Foliar half-life and distribution for potatoes					N.A.
None	Runoff and Erosion predictions for apple/potato/cotton					N.A.
None	Risk assessment for apple/potato/cotton					N.A.
None	PELMO Modeling - sugarbeet/Germany					N.A.
Toxicology, Section 158.340						
		42055331	3125	PER	Report No. 100040 (TGAI)	
		42256313	3125	PER	Report No. 100010 (2 F)	
		43428201	3125	PER	Report No. 106380 (1.6 F)	
		43679601	1156	OWN	Report No. 74585 (Adv)	
81-1	Acute oral toxicity rat		11556	OWN	Report No. 75195 (Adv Plus)	Submitted with application for Advantage Plus® 9 for Cats

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
401 M Street, S.W.
WASHINGTON, D.C. 20460 Form

Approved OMB No. 2070-0060

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DATA MATRIX REA

Date: April 7, 2000	**EPA Reg No./File Symbol:** 11556-~~XXX~~, 11556-XXX	Page 5 of 10
Bayer Corporation - Agriculture Division, Animal Health P.O. Box 390 Shawnee Mission, KS 66201-0390	**Product:** Advantage Plus® 9 for Cats Advantage Plus® 18 for Cats	**Ingredient:** Imidacloprid, CAS = 138261-41-3 Pyriproxyfen, CAS = 95737-68-1

Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note: Report Number	Description
81-2	Acute dermal toxicity, rat/rabbit	42055332	3125	PER	Report No. 100041 (TGAI)	
		42256315	3125	PER	Report No. 100002 (2 F)	
		43428201	3125	PER	Report No. 106380 (1.6 F	
		4379602	11556	OWN	Report No. 74584 (Adv)	
			11556	OWN	Report No. 75196	Submitted with application for Advantage Plus® 9 for Cats
81-3	Acute inhalation toxicity, rat	42055333	3125	PER	Report No. 99806 (TGAI)	
		42286101	3125	PER	Report No. 99806-1 (TGAI)	
		42256317	3125	PER	Report No. 100012 (2 F)	
		43428201	3125	PER	Report No. 106380 (1.6 F)	
		43679603	11556	OWN	Report No. 74589 (Adv)	
			11556	OWN	Report No. 75197 (Adv Plus)	Submitted with application for Advantage Plus® 9 for Cats
81-4	Primary eye irritation - rabbit	42055334	3125	PER	Report No. 99679 (TGAI)	
		42256319	3125	PER	Report No. 99815 (2 F)	
		43428201	3125	PER	Report No. 106380 (1.6 F)	
		43428201	3125	PER	Report No. 106380 (1.6 F)	
		43679604	11556	OWN	Report No. 74588 (Adv)	
			11556	OWN	Report No. 75199 (Adv Plus)	Submitted with application for Advantage Plus® 9 for Cats

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DATA MATRIX

Date: April 7, 2000	**EPA Reg No./File Symbol:** 11556-~~XXX~~ PEA, 11556-XXX	Page 6 of 10
Bayer Corporation - Agriculture Division, Animal Health P.O. Box 390 Shawnee Mission, KS 66201-0390	**Product:** Advantage Plus® 9 for Cats Advantage Plus® 18 for Cats	**Ingredient:** Imidacloprid, CAS = 138261-41-3 Pyriproxyfen, CAS = 95737-68-1

Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note: Report Number	Description
81-5	Primary dermal irritation - rabbit	42055335	3125	PER	Report No. 99804 (TGAI)	
		42256321	3125	PER	Report No. 99816 (2 F)	
		43428201	3125	PER	Report No. 106380 (1.6 F)	
		43679605	11556	OWN	Report No. 74586 (Adv)	
			11556	OWN	Report No. 75200 (Adv Plus)	Submitted with application for Advantage Plus® 9 for Cats
81-6	Dermal sensitization - guinea pig	42055336	3125	PER	Report No. 99800 (TGAI)	
		42256323	3125	PER	Report No. 100003 (2 F)	
		43428201	3125	PER	Report No. 106380 (1.6 F)	
		43679606	11556	OWN	Report No. 74587 (Adv)	
			11556	OWN	Report No. 75201 (Adv Plus)	Submitted with application for Advantage Plus® 9 for Cats
81-8(SS)	Acute neurotoxicity	43170301	3125	PER	Report No. 106348	
		43285801	3125	PER	Report No. 106348-1	
82-1(a)	90-day feeding - rodent	42256327	3125	PER	Report No. 100036	
82-1(b)	90-day feeding - non-rodent	42256328	3125	PER	Report No. 100176	
82-2	21-day dermal - rabbit/rat	42256329	3125	PER	Report No. 100688	
82-5(b)	90 day neurotoxicity - mammal	43286401	3125	PER	Report No. 106356	
83-1(a)	Chronic feeding toxicity - rodent	42256331	3125	PER	Report No. 100652	
		42256332	3125	PER	Report No. 101931	
		42256333	3125	PER	Report No. 102658	
		42256334	3125	PER	Report No. 99672	
83-1(b)	Chronic feeding toxicity - non-rodent	42273002	3125	PER	Report No. 100015	

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Date: April 7, 2000	**EPA Reg No./File Symbol:** 11556-~~EUC~~, 11556-XXX (PE4)	Page 7 of 10
Bayer Corporation - Agriculture Division, Animal Health P.O. Box 390 Shawnee Mission, KS 66201-0390	**Product:** Advantage Plus® 9 for Cats Advantage Plus® 18 for Cats	**Ingredient:** Imidacloprid, CAS = 138261-41-3 Pyriproxyfen, CAS = 95737-68-1

Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note / Report Number	Description
		42256331	3125	PER	Report No. 100652	
		42256332	3125	PER	Report No. 101931	
		42256333	3125	PER	Report No. 102658	
83-2(a)	Oncogenicity - rat	42256334	3125	PER	Report No. 99672	
		42256335	3125	PER	Report No. 100693	
		42256336	3125	PER	Report No. 101929	
83-2(b)	Oncogenicity - mouse	42256337	3125	PER	Report No. 99808	
83-3(a)	Developmental toxicity - rat	42256338	3125	PER	Report No. 98571	
83-3(b)	Developmental toxicity - rabbit	42256339	3125	PER	Report No. 98572	
83-4	Two generation reproduction - rat	42256340	3125	PER	Report No. 100647	
		42256341	3125	PER	Report No. 101276	
		42256342	3125	PER	Report No. 98584	
84-2(a)	Gene mutation (ames test)	42256343	3125	PER	Report No. 98570	
		42256344	3125	PER	Report No. 100021	
		42256345	3125	PER	Report No. 99262	
		42256346	3125	PER	Report No. 99257	
		42256347	3125	PER	Report No. 102652	
	Structural chromosomal aberration	42256348	3125	PER	Report No. 102654	
84-2(b)		42256349	3125	PER	Report No. 102655	
		42256350	3125	PER	Report No. 99676	
		42256351	3125	PER	Report No. 101275	
		42256352	3125	PER	Report No. 98573	
84-4	Other genotoxic effects	42256353	3125	PER	Report No. 102653	

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Bayer Corporation - Agriculture Division, Animal Health P.O. Box 390 Shawnee Mission, KS 66201-0390	**Product:** Advantage Plus® 9 for Cats Advantage Plus® 18 for Cats	**Ingredient:** Imidacloprid, CAS = 138261-41-3 Pyriproxyfen, CAS = 95737-68-1

Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note / Report Number	Description
		42256354	3125	PER	Report No. 101999	
		42256355	3125	PER	Report No. 87264	
		42256356	3125	PER	Report No. 87265	
85-1	General metabolism	42256357	3125	PER	Report No. 102617	
		43679501	11556	OWN	Report No. 74579 (Adv)	Cats
		43679502	11556	OWN	Report No. 74591 (Adv)	Cats
		44157301	11556	OWN	Report No. 74746 (Adv)	Kittens
870.7200		44157302	11556	OWN	Report No. 74747 (Adv)	Kittens
(86-1)	Domestic Animal Safety		11556	OWN	Report No. 75122 (Adv Plus)	Cats, submitted with application for Advantage Plus® 9 for Cats
		43679503	11556	OWN	Report No. 74571 (Adv)	Cats
		43679504	11556	OWN	Report No. 74581 (Adv)	Cats
		43679609	11556	OWN	Report No. 74572 (Adv)	Dogs
		43679610	11556	OWN	Report No. 74541 (Adv)	Dogs
		44256901	11556	OWN	Report No. 74800 (Adv)	Speed of flea kill
		44256902	11556	OWN	Report No. 47828 (Adv)	Larvicidal efficacy
		44256903	11556	OWN	Report No. 74792 (Adv)	Effects of shampooing
			1021	PER	Report No. OT018-94	Pyriproxyfen efficacy
			1021	PER	Report No. OT016-93	Pyriproxyfen efficacy
			1021	PER	Report No. OT006-96	Pyriproxyfen efficacy
95-9	Efficacy		1021	PER	Report No. OT023-93	Pyriproxyfen efficacy
Plant Protection, Section 158.540						
122-2	Aquatic plant growth					N.A.
123-2	Aquatic plant growth					N.A.

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Bayer Corporation - Agriculture Division, Animal Health P.O. Box 390 Shawnee Mission, KS 66201-0390	**Product:** Advantage Plus® 9 for Cats Advantage Plus® 18 for Cats	**Ingredient:** Imidacloprid, CAS = 138261-41-3 Pyriproxyfen, CAS = 95737-68-1

Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note / Report Number	Description
Non-Target Insects, Section 158.590						
141-1	Honey bee acute contact					N.A.
141-2	Honey bee residue on foliage					N.A.
Reentry Protection, Section 158.390						
230-236	Mixer/loader/applicator exposure					N. A.
Environmental Fate, Section 158.290						
161-1	Hydrolysis					N.A.
161-2	Photodegradation - water					N.A.
161-3	Photodegradation - soil					N.A.
162-1	Aerobic soil metabolism					N.A.
162-2	Anerobic soil metabolism					N.A.
162-3	Anaerobic aquatic metabolism					N.A.
163-1	Leaching / adsorption/desorption					N.A.
164-1	Terrestrial field dissipation					N.A.
165-1	Confined rotational crop					N.A.
165-2	Field rotational crop					N.A.
166-1	Ground water - small prospective					N.A.
None	Environmental fate summary					N.A.
Residue, Section 158.240						
171-4(a)	Nature of residue - plants					N.A.
171-4(b)	Nature of residue - livestock and poultry					N.A.
171-4(c)	Residue analytical method - plants					N.A.
171-4(d)	Residue analytical method - animal					N.A.
171-4(e)	Storage stability					N.A.
171-4(j)	Magnitude of residues - meat/milk/poultry/egg					N.A.

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Bayer Corporation - Agriculture Division, Animal Health P.O. Box 390 Shawnee Mission, KS 66201-0390	**Product:** Advantage Plus® 9 for Cats Advantage Plus® 18 for Cats	**Ingredient:** Imidacloprid, CAS = 138261-41-3 Pyriproxyfen, CAS = 95737-68-1

Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note Report Number	Description
171-4(k)	Magnitude of residue - crop field trials					N.A.
171-4(l)	Magnitude of residue - processed food/feed					N.A.
171-4(m)	Method validation/ multiresidue method					N.A.
None	Benefits Reports					
None	Dietary Analysis					N.A.

Signature F. Terry McNamara — F. Terry McNamara, Manager, Preclinical Development — April 7, 2000

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Bayer Corporation - Agriculture Division, Animal Health P.O. Box 390 Shawnee Mission, KS 66201-0390	**Product:** Advantage Plus® 9 for Cats Advantage Plus® 18 for Cats	**Ingredient:** Imidacloprid, CAS = 138261-41-3 Pyriproxyfen, CAS = 95737-68-1

Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note: Report Number	Note: Description
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			11556	OWN		Submitted with application for Advantage Plus® 9 for Cats

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			3125	PER		
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			3125	PER		
			3125	PER		
			3125	PER		
			3125	PER		
			3125	PER		
						N.A . - Does not dissociate
			3125	PER		
			3125	PER		
			3125	PER		
			3125	PER		
			3125	PER		
			3125	PER		N.A. - No oxidative or reductive characteristics
			3125	PER		
			3125	PER		

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Bayer Corporation - Agriculture Division, Animal Health P.O. Box 390 Shawnee Mission, KS 66201-0390	**Product:** Advantage Plus® 9 for Cats Advantage Plus® 18 for Cats	**Ingredient:** Imidacloprid, CAS = 138261-41-3 Pyriproxyfen, CAS = 95737-68-1

Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note / Report Number	Description
			3125	PER		
			3125	PER		
			3125	PER		N.A. - Solid
			3125	PER		N.A. - Solid
			3125	PER		
			3125	PER		
						N.A. - Solid
			11556	OWN		Submitted with application for Advantage Plus® 9 for Cats
			11556	OWN		Submitted with application for Advantage Plus® 9 for Cats
						N.A.
						N.A.
						N.A.
						N.A.
						N.A.
						N.A.
						N.A.
						N.A.
						N.A.

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Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note: Report Number	Note: Description
						N.A.
						N.A.
						N.A.
						N.A.
						N.A.
						N.A.
						N.A.
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			3125	PER		
			3125	PER		
			3125	PER		
			11556	OWN		
			11556	OWN		Submitted with application for Advantage Plus® 9 for Cats
			3125	PER		
			3125	PER		
			3125	PER		
			3125	PER		
			11556	OWN		
			11556	OWN		Submitted with application for Advantage Plus® 9 for Cats
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			11556	OWN		
			11556	OWN		Submitted with application for Advantage Plus® 9 for Cats

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Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note: Report Number	Note: Description
[redacted]			3125	PER		
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Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note / Report Number	Description
[redacted]	[redacted]	[redacted]	3125	PER	[redacted]	
[redacted]	[redacted]	[redacted]	3125	PER	[redacted]	
[redacted]	[redacted]	[redacted]	3125	PER	[redacted]	
[redacted]	[redacted]	[redacted]	3125	PER	[redacted]	
[redacted]	[redacted]	[redacted]	3125	PER	[redacted]	
[redacted]	[redacted]	[redacted]	3125	PER	[redacted]	
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DATA MATRIX REA

Date: April 7, 2000	**EPA Reg No./File Symbol:** 11556-~~XXX~~, 11556-XXX	Page 8 of 10
Bayer Corporation - Agriculture Division, Animal Health P.O. Box 390 Shawnee Mission, KS 66201-0390	**Product:** Advantage Plus® 9 for Cats Advantage Plus® 18 for Cats	**Ingredient:** Imidacloprid, CAS = 138261-41-3 Pyriproxyfen, CAS = 95737-68-1

Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note / Report Number	Description
			3125	PER		
			3125	PER		
			3125	PER		
			3125	PER		
			11556	OWN		Cats
			11556	OWN		Cats
			11556	OWN		Kittens
			11556	OWN		Kittens
			11556	OWN		Cats, submitted with application for Advantage Plus® 9 for Cats
			11556	OWN		Cats
			11556	OWN		Cats
			11556	OWN		Dogs
			11556	OWN		Dogs
			11556	OWN		Speed of flea kill
			11556	OWN		Larvicidal efficacy
			11556	OWN		Effects of shampooing
			1021	PER		Pyriproxyfen efficacy
			1021	PER		Pyriproxyfen efficacy
			1021	PER		Pyriproxyfen efficacy
			1021	PER		Pyriproxyfen efficacy
						N.A.
						N.A.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
401 M Street, S.W.
WASHINGTON, D.C. 20460 Form

Approved OMB No. 2070-0060

Paperwork Reduction Act Notice: The public reporting burden for this collection of information is estimated to average 0.25 hours per response for registration activities and .025 hours per response for information, including suggestions for reducing the burden to: Director, OPPE Information Management Division (2137), U.S. Environmental Protection Agency, 401 M Street, S.W., Washington, DC 20460. Do not send the form to the address.

DATA MATRIX

Date: April 7, 2000	**EPA Reg No./File Symbol:** 11556-[redacted], 11556-XXX REA	Page 9 of 10
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Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note: Report Number	Note: Description
[redacted]						N.A.
						N.A.
						N. A.
						N.A.
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Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note / Report Number	Description
[redacted]					[redacted]	N.A.
						N.A.
						N.A.

Signature F. Terry McNamara

F. Terry McNamara
Manager, Preclinical Development

April 7, 2000

EPA Form 8570-35 (9-97) Electronic Paper versions available. Submit only Paper version. Agency Internal Use Copy

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(Front Panel)

Advantage Plus® 9

Topical Solution

Once-A-Month Topical Flea Treatment for Cats and Kittens 7 Months and Older and 9 lbs. and Under

READ THE ENTIRE LABEL BEFORE EACH USE

For the Prevention and Treatment of Flea Infestations

- Available Only Through Licensed Practicing Veterinarians
- Kills 98-100% of the Fleas on Cats Within 12 Hours
- Kills Reinfesting Fleas Within 2 Hours
- One Treatment Prevents Further Flea Infestation For Up to Four Weeks
- Kills Adult Fleas, Eggs, and Larvae
- Prevents Immature Fleas from Developing into Biting, Breeding Adults
- Provides 3-way Protection Against Fleas, Breaking Life Cycle at Egg, Larval, and Adult Stages

Active Ingredients	% By Weight
Imidacloprid; 1-[(6-Chloro-3-pyridinyl) methyl]-N-nitro-2-imidazolidinimine . .	9.10%
Pyriproxyfen; 2-[1-methyl-2-(4-phenoxyphenoxy)ethoxy] pyridine	0.46%
Inert Ingredients	90.44%
Total	100.00%

KEEP OUT OF REACH OF CHILDREN

CAUTION

See Below for First Aid and Precautionary Statements

PRECAUTIONARY STATEMENTS
HAZARDS TO HUMANS

Harmful if swallowed. Causes moderate eye irritation. Avoid contact with eyes or clothing. Wash hands thoroughly with soap and warm water after handling.

HAZARDS TO DOMESTIC ANIMALS

For external use only.
Do not use on kittens under 7 months of age.

As with any product, consult your veterinarian before using this product on debilitated, aged, pregnant or nursing animals. Individual sensitivities, while rare, may occur after using ANY pesticide product for pets. If signs persist, or become more severe, consult a veterinarian immediately. If your animal is on medication, consult your veterinarian before using this or any other product. For consumer questions call 1-800-255-6826. For medical emergencies call 1-877-258-2280.

FIRST AID

If in eyes: Hold eye open and rinse slowly and gently with water for 15-20 minutes. Remove contact lenses, if present, after the first 5 minutes, then continue rinsing eye. Call a poison control center or doctor for treatment advice.

If swallowed: Call a Poison Control Center or doctor immediately for treatment advice. Have person sip a glass of water if able to swallow. Do not induce vomiting unless told to do so by the poison control center or doctor. Do not give anything to an unconscious person.

If on skin: Wash with plenty of soap and water.

To Physician: Treat the patient symptomatically.

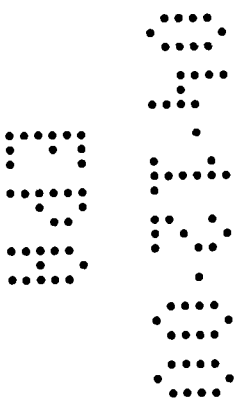
Four 0.4 mL Tubes

EPA Est. 11556-DEU-1
EPA Reg. No. 11556-XXX

Manufactured For

Bayer Corporation
Agriculture Division
Animal Health
Shawnee Mission, Kansas 66201 USA

Made in Germany



(Back Panel)

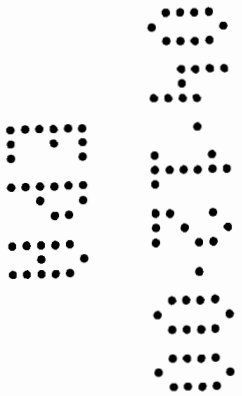
Advantage Plus® 9

Topical Solution
Fast
Effective
Multi-Stage Flea Control

Once-A-Month Topical Flea Treatment for Cats and Kittens 7 Months and Older and 9 lbs. and Under

- Available only through licensed practicing veterinarians
- Kills fleas within 12 hours
- Kills reinfesting fleas within 2 hours
- Prevents reinfestation for up to 4 weeks
- Convenient, easy to apply
- Kills adult fleas, eggs and larvae

Four 0.4 mL Tubes



(Inside Left Panel)

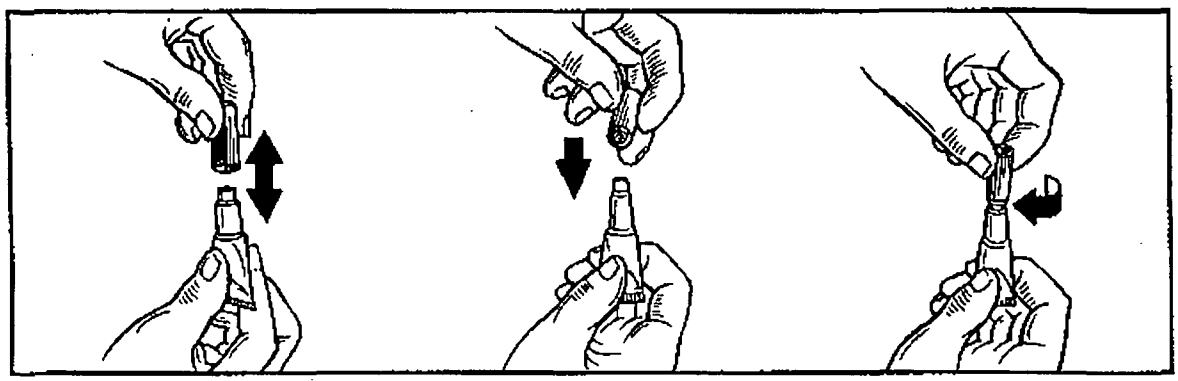
For the Prevention and Treatment of Flea Infestation on Cats and Kittens 7 Months and Older and 9 lbs and Under.

DIRECTIONS FOR USE

It is a violation of Federal Law to use this product in a manner inconsistent with its labeling.

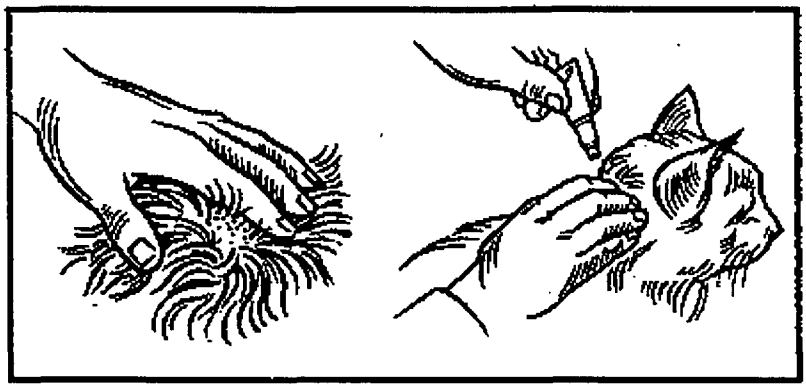
HOW TO APPLY

1. Use only on cats. Do not use on other animals.
2. Remove one applicator tube from the package.



3. Hold applicator tube in an upright position. Pull cap off tube.
4. Turn the cap around and place other end of cap back on tube.
5. Twist cap to break seal, then remove cap from tube.

6. Part the hair in the neck at the base of the skull until the skin is visible. Place the tip of the tube on the skin and squeeze the tube twice to expel the entire contents of the tube directly on the skin. Do not get this product in your pet's eyes or mouth. The product is bitter tasting and salivation may occur for a short time if the cat licks the product immediately after treatment. Treatment at the base of the skull will minimize the opportunity for the cat to lick the product.



7. Discard empty tube as described in Storage and Disposal.

(Inside Right Panel)

Advantage Plus® 9

Topical Solution

Once-a-Month topical flea treatment for cats and kittens 7 months and older and 9 lbs. and under.

The successive feeding activity of fleas on pets frequently elicits a hypersensitivity skin disorder known as flea allergy dermatitis (FAD). Treatment of pets with Advantage Plus® rapidly kills fleas and reduces the incidence of this condition.

Advantage Plus® kills 98-100% of the existing fleas on pets within 12 hours. Reinfesting fleas are killed within 2 hours with protection against further flea infestation lasting for up to four (4) weeks. Pre-existing pupae in the environment may continue to emerge for six (6) weeks or longer depending upon the climatic conditions.

Fleas, eggs and larvae in the pet's surroundings are killed following contact with an Advantage Plus® treated pet. Advantage Plus® provides multi-stage flea control effectively breaking all flea life-cycle stages for quick and lasting control of flea populations.

Advantage Plus® kills adult fleas quickly, inhibits the development of immature flea life stages and prevents them from reaching the biting adult stage.

Advantage Plus® remains efficacious following a shampoo treatment, swimming or after exposure to rain or sunlight.

Monthly treatments are required for optimal control and prevention of fleas.

If re-treatment becomes necessary earlier than four weeks, do not re-treat more than once weekly.

STORAGE AND DISPOSAL

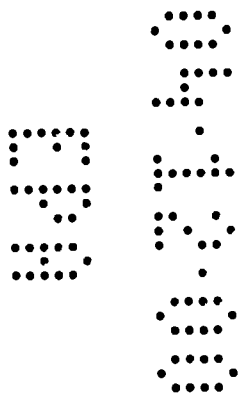
Do not contaminate water, food or feed by storage or disposal.

Storage: Store in a cool, dry place. **Pesticide Disposal**: Securely wrap original container in several layers of newspaper and discard in trash. **Container Disposal**: Do not reuse empty container. Wrap container and put in trash.

LIMITED WARRANTY AND LIMITATION OF DAMAGES

Bayer Corporation, Agriculture Division, Animal Health warrants that this material conforms to the chemical description on the label. BAYER CORPORATION MAKES NO OTHER EXPRESS OR IMPLIED WARRANTY, INCLUDING ANY OTHER EXPRESS OR IMPLIED WARRANTY OF FITNESS OR MERCHANTABILITY, and no agent of Bayer Corporation is authorized to do so except in writing with a specific reference to this warranty. Any damages arising from a breach of this warranty shall be limited to direct damages and shall not include consequential commercial damages such as loss of profits or values, etc.

Use these calendar stickers to remind you when your pet is due for its next monthly application of Advantage Plus®.



(Label on Individual Tube)

Advantage Plus®

9.10% Imidacloprid

0.46% Pyriproxyfen

0.4 mL

EPA Reg. No. 11556-XXX

CAUTION

Keep Out of Reach of Children

Read The Entire Label Before Use

BAYER

Lot No. 0000000

(Front Panel)

Advantage Plus® 9

Topical Solution

Once-A-Month Topical Flea Treatment for Cats and Kittens 7 Months and Older and 9 lbs. and Under

READ THE ENTIRE LABEL BEFORE EACH USE

For the Prevention and Treatment of Flea Infestations

- Available Only Through Licensed Practicing Veterinarians
- Kills 98-100% of the Fleas on Cats Within 12 Hours
- Kills Reinfesting Fleas Within 2 Hours
- One Treatment Prevents Further Flea Infestation For Up to Four Weeks
- Kills Adult Fleas, Eggs, and Larvae
- Prevents Immature Fleas from Developing into Biting, Breeding Adults
- Provides 3-way Protection Against Fleas, Breaking Life Cycle at Egg, Larval, and Adult Stages

Active Ingredients	% By Weight
Imidacloprid; 1-[(6-Chloro-3-pyridinyl) methyl]-N-nitro-2-imidazolidinimine . .	9.10%
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Inert Ingredients	90.44%
Total	100.00%

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CAUTION

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PRECAUTIONARY STATEMENTS
HAZARDS TO HUMANS

Harmful if swallowed. Causes moderate eye irritation. Avoid contact with eyes or clothing. Wash hands thoroughly with soap and warm water after handling.

HAZARDS TO DOMESTIC ANIMALS

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Do not use on kittens under 7 months of age.

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If on skin: Wash with plenty of soap and water.

To Physician: Treat the patient symptomatically.

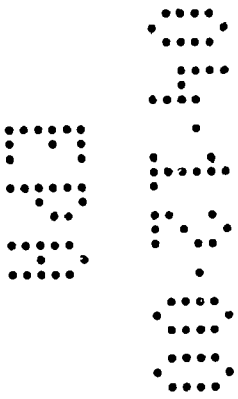
Four 0.4 mL Tubes

EPA Est. 11556-DEU-1
EPA Reg. No. 11556-XXX

Manufactured For

Bayer Corporation
Agriculture Division
Animal Health
Shawnee Mission, Kansas 66201 USA

Made in Germany



(Back Panel)

Advantage Plus® 9

Topical Solution
Fast
Effective
Multi-Stage Flea Control

Once-A-Month Topical Flea Treatment for Cats and Kittens 7 Months and Older and 9 lbs. and Under

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- Kills adult fleas, eggs and larvae

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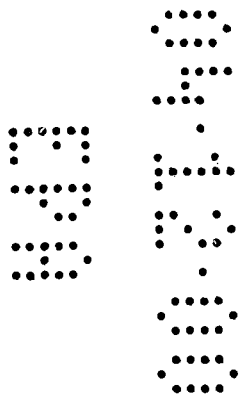


(Inside Left Panel)

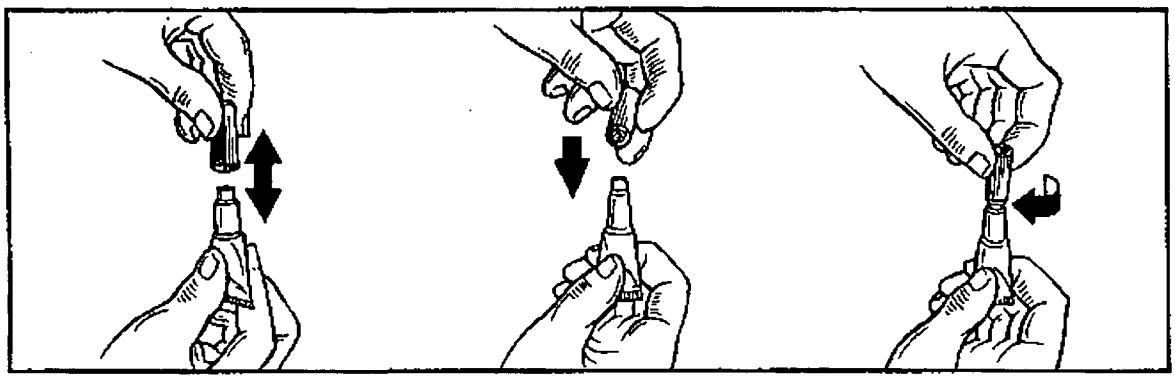
For the Prevention and Treatment of Flea Infestation on Cats and Kittens 7 Months and Older and 9 lbs and Under.

DIRECTIONS FOR USE

It is a violation of Federal Law to use this product in a manner inconsistent with its labeling.

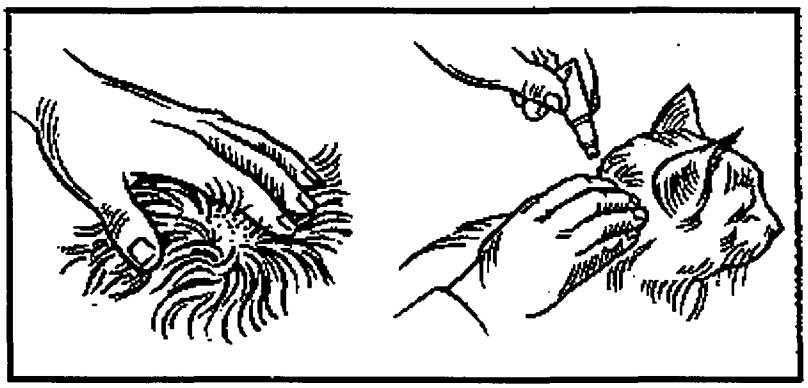
HOW TO APPLY

1. Use only on cats. Do not use on other animals.
2. Remove one applicator tube from the package.



3. Hold applicator tube in an upright position. Pull cap off tube.
4. Turn the cap around and place other end of cap back on tube.
5. Twist cap to break seal, then remove cap from tube.

6. Part the hair in the neck at the base of the skull until the skin is visible. Place the tip of the tube on the skin and squeeze the tube twice to expel the entire contents of the tube directly on the skin. Do not get this product in your pet's eyes or mouth. The product is bitter tasting and salivation may occur for a short time if the cat licks the product immediately after treatment. Treatment at the base of the skull will minimize the opportunity for the cat to lick the product.



7. Discard empty tube as described in Storage and Disposal.

(Inside Right Panel)

Advantage Plus® 9

Topical Solution

Once-a-Month topical flea treatment for cats and kittens 7 months and older and 9 lbs. and under.

The successive feeding activity of fleas on pets frequently elicits a hypersensitivity skin disorder known as flea allergy dermatitis (FAD). Treatment of pets with Advantage Plus® rapidly kills fleas and reduces the incidence of this condition.

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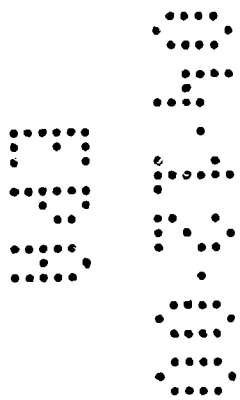

(Label on Individual Tube)

Advantage Plus®

9.10% Imidacloprid

0.46% Pyriproxyfen

0.4 mL

EPA Reg. No. 11556-XXX

CAUTION

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BAYER

Lot No. 0000000

(Front Panel)

Advantage Plus® 9

Topical Solution

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Inert Ingredients	90.44%
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If on skin: Wash with plenty of soap and water.

To Physician: Treat the patient symptomatically.

Four 0.4 mL Tubes

EPA Est. 11556-DEU-1
EPA Reg. No. 11556-XXX

Manufactured For

Bayer Corporation
Agriculture Division
Animal Health
Shawnee Mission, Kansas 66201 USA

Made in Germany

(Back Panel)

Advantage Plus® 9

Topical Solution
Fast
Effective
Multi-Stage Flea Control

Once-A-Month Topical Flea Treatment for Cats and Kittens 7 Months and Older and 9 lbs. and Under

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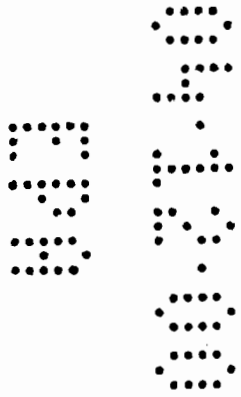


(Inside Left Panel)

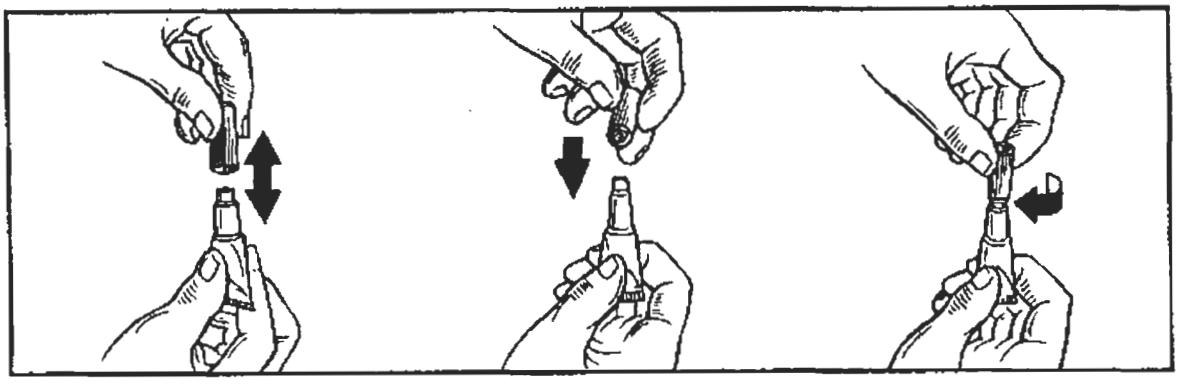
For the Prevention and Treatment of Flea Infestation on Cats and Kittens 7 Months and Older and 9 lbs and Under.

DIRECTIONS FOR USE

It is a violation of Federal Law to use this product in a manner inconsistent with its labeling.

HOW TO APPLY

1. Use only on cats. Do not use on other animals.
2. Remove one applicator tube from the package.



3. Hold applicator tube in an upright position. Pull cap off tube.
4. Turn the cap around and place other end of cap back on tube.
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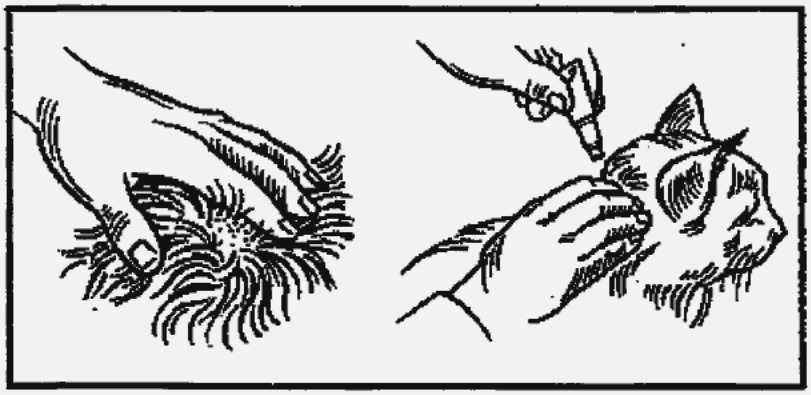
6. Part the hair in the neck at the base of the skull until the skin is visible. Place the tip of the tube on the skin and squeeze the tube twice to expel the entire contents of the tube directly on the skin. Do not get this product in your pet's eyes or mouth. The product is bitter tasting and salivation may occur for a short time if the cat licks the product immediately after treatment. Treatment at the base of the skull will minimize the opportunity for the cat to lick the product.



7. Discard empty tube as described in Storage and Disposal.

(Inside Right Panel)

Advantage Plus® 9

Topical Solution

Once-a-Month topical flea treatment for cats and
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Advantage Plus® kills adult fleas quickly, inhibits the development of immature flea life stages and prevents them from reaching the biting adult stage.

Advantage Plus® remains efficacious following a shampoo treatment, swimming or after exposure to rain or sunlight.

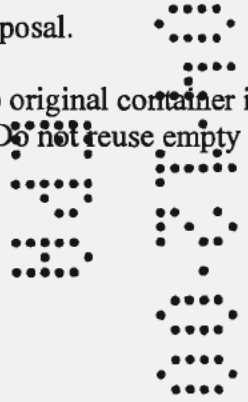
Monthly treatments are required for optimal control and prevention of fleas.

If re-treatment becomes necessary earlier than four weeks, do not re-treat more than once weekly.

STORAGE AND DISPOSAL

Do not contaminate water, food or feed by storage or disposal.

Storage: Store in a cool, dry place. **Pesticide Disposal**: Securely wrap original container in several layers of newspaper and discard in trash. **Container Disposal**: Do not reuse empty container. Wrap container and put in trash.



LIMITED WARRANTY AND LIMITATION OF DAMAGES

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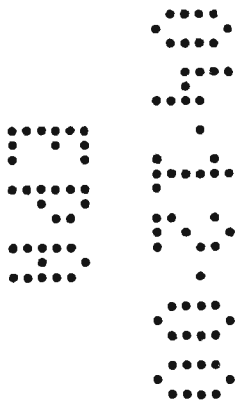
Use these calendar stickers to remind you when your pet is due for its next monthly application of Advantage Plus®.



(Label on Individual Tube)

Advantage Plus®

9.10% Imidacloprid

0.46% Pyriproxyfen

0.4 mL

EPA Reg. No. 11556-XXX

CAUTION

Keep Out of Reach of Children

Read The Entire Label Before Use

BAYER

Lot No. 0000000

(Front Panel)

Advantage Plus® 9

Topical Solution

Once-A-Month Topical Flea Treatment for Cats and Kittens 7 Months and Older and 9 lbs. and Under

READ THE ENTIRE LABEL BEFORE EACH USE

For the Prevention and Treatment of Flea Infestations

- Available Only Through Licensed Practicing Veterinarians
- Kills 98-100% of the Fleas on Cats Within 12 Hours
- Kills Reinfesting Fleas Within 2 Hours
- One Treatment Prevents Further Flea Infestation For Up to Four Weeks
- Kills Adult Fleas, Eggs, and Larvae
- Prevents Immature Fleas from Developing into Biting, Breeding Adults
- Provides 3-way Protection Against Fleas, Breaking Life Cycle at Egg, Larval, and Adult Stages

Active Ingredients	% By Weight
Imidacloprid; 1-[(6-Chloro-3-pyridinyl) methyl]-N-nitro-2-imidazolidinimine . .	9.10%
Pyriproxyfen; 2-[1-methyl-2-(4-phenoxyphenoxy)ethoxy] pyridine	0.46%
Inert Ingredients	90.44%
Total	100.00%

KEEP OUT OF REACH OF CHILDREN

CAUTION

See Below for First Aid and Precautionary Statements

PRECAUTIONARY STATEMENTS
HAZARDS TO HUMANS

Harmful if swallowed. Causes moderate eye irritation. Avoid contact with eyes or clothing. Wash hands thoroughly with soap and warm water after handling.

HAZARDS TO DOMESTIC ANIMALS

For external use only.
Do not use on kittens under 7 months of age.

As with any product, consult your veterinarian before using this product on debilitated, aged, pregnant or nursing animals. Individual sensitivities, while rare, may occur after using ANY pesticide product for pets. If signs persist, or become more severe, consult a veterinarian immediately. If your animal is on medication, consult your veterinarian before using this or any other product. For consumer questions call 1-800-255-6826. For medical emergencies call 1-877-258-2280.

FIRST AID

If in eyes: Hold eye open and rinse slowly and gently with water for 15-20 minutes. Remove contact lenses, if present, after the first 5 minutes, then continue rinsing eye. Call a poison control center or doctor for treatment advice.

If swallowed: Call a Poison Control Center or doctor immediately for treatment advice. Have person sip a glass of water if able to swallow. Do not induce vomiting unless told to do so by the poison control center or doctor. Do not give anything to an unconscious person.

If on skin: Wash with plenty of soap and water.

To Physician: Treat the patient symptomatically.

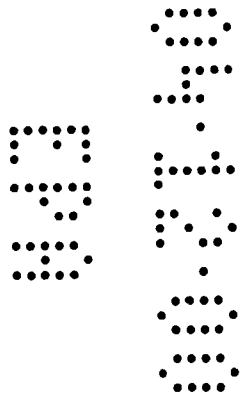
Four 0.4 mL Tubes

EPA Est. 11556-DEU-1
EPA Reg. No. 11556-XXX

Manufactured For

Bayer Corporation
Agriculture Division
Animal Health
Shawnee Mission, Kansas 66201 USA

Made in Germany



(Back Panel)

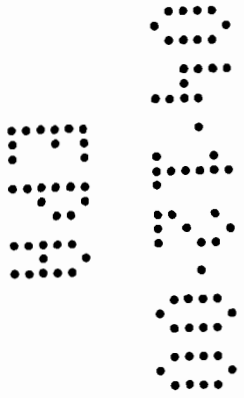
Advantage Plus® 9

Topical Solution
Fast
Effective
Multi-Stage Flea Control

Once-A-Month Topical Flea Treatment for Cats and Kittens 7 Months and Older and 9 lbs. and Under

- Available only through licensed practicing veterinarians
- Kills fleas within 12 hours
- Kills reinfesting fleas within 2 hours
- Prevents reinfestation for up to 4 weeks
- Convenient, easy to apply
- Kills adult fleas, eggs and larvae

Four 0.4 mL Tubes



(Inside Left Panel)

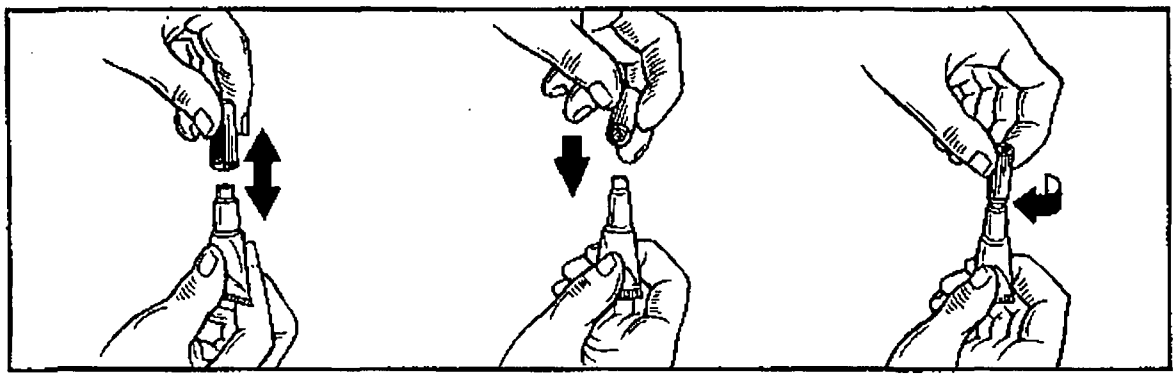
For the Prevention and Treatment of Flea Infestation on Cats and Kittens 7 Months and Older and 9 lbs and Under.

DIRECTIONS FOR USE

It is a violation of Federal Law to use this product in a manner inconsistent with its labeling.

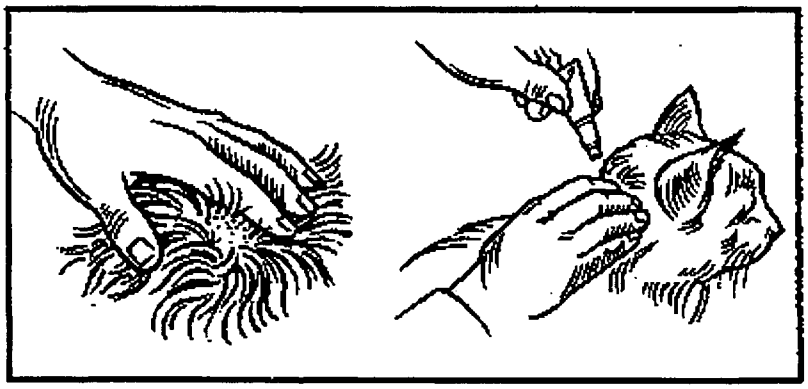
HOW TO APPLY

1. Use only on cats. Do not use on other animals.
2. Remove one applicator tube from the package.



3. Hold applicator tube in an upright position. Pull cap off tube.
4. Turn the cap around and place other end of cap back on tube.
5. Twist cap to break seal, then remove cap from tube.

6. Part the hair in the neck at the base of the skull until the skin is visible. Place the tip of the tube on the skin and squeeze the tube twice to expel the entire contents of the tube directly on the skin. Do not get this product in your pet's eyes or mouth. The product is bitter tasting and salivation may occur for a short time if the cat licks the product immediately after treatment. Treatment at the base of the skull will minimize the opportunity for the cat to lick the product.



7. Discard empty tube as described in Storage and Disposal.

(Inside Right Panel)

Advantage Plus® 9

Topical Solution

Once-a-Month topical flea treatment for cats and
kittens 7 months and older and 9 lbs. and under.

The successive feeding activity of fleas on pets frequently elicits a hypersensitivity skin disorder known as flea allergy dermatitis (FAD). Treatment of pets with Advantage Plus® rapidly kills fleas and reduces the incidence of this condition.

Advantage Plus® kills 98-100% of the existing fleas on pets within 12 hours. Reinfesting fleas are killed within 2 hours with protection against further flea infestation lasting for up to four (4) weeks. Pre-existing pupae in the environment may continue to emerge for six (6) weeks or longer depending upon the climatic conditions.

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STORAGE AND DISPOSAL

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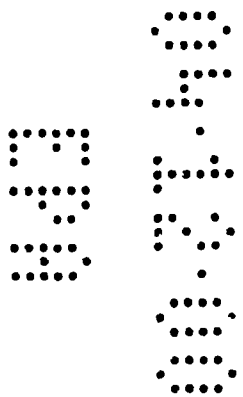

(Label on Individual Tube)

Advantage Plus®

9.10% Imidacloprid

0.46% Pyriproxyfen

0.4 mL

EPA Reg. No. 11556-XXX

CAUTION

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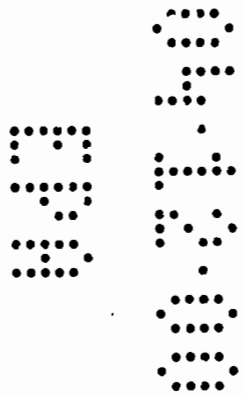
Read The Entire Label Before Use

BAYER

Lot No. 0000000



(Front Panel)

Advantage Plus® 9

Topical Solution

Once-A-Month Topical Flea Treatment for Cats and Kittens 7 Months and Older and 9 lbs. and Under

READ THE ENTIRE LABEL BEFORE EACH USE

For the Prevention and Treatment of Flea Infestations

- Available Only Through Licensed Practicing Veterinarians
- Kills 98-100% of the Fleas on Cats Within 12 Hours
- Kills Reinfesting Fleas Within 2 Hours
- One Treatment Prevents Further Flea Infestation For Up to Four Weeks
- Kills Adult Fleas, Eggs, and Larvae
- Prevents Immature Fleas from Developing into Biting, Breeding Adults
- Provides 3-way Protection Against Fleas, Breaking Life Cycle at Egg, Larval, and Adult Stages

Active Ingredients	% By Weight
Imidacloprid; 1-[(6-Chloro-3-pyridinyl) methyl]-N-nitro-2-imidazolidinimine . .	9.10%
Pyriproxyfen; 2-[1-methyl-2-(4-phenoxyphenoxy)ethoxy] pyridine	0.46%
Inert Ingredients	90.44%
Total	100.00%

KEEP OUT OF REACH OF CHILDREN

CAUTION

See Below for First Aid and Precautionary Statements

PRECAUTIONARY STATEMENTS
HAZARDS TO HUMANS

Harmful if swallowed. Causes moderate eye irritation. Avoid contact with eyes or clothing. Wash hands thoroughly with soap and warm water after handling.

HAZARDS TO DOMESTIC ANIMALS

For external use only.
Do not use on kittens under 7 months of age.

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FIRST AID

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If on skin: Wash with plenty of soap and water.

To Physician: Treat the patient symptomatically.

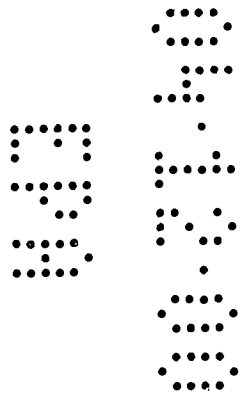
Six 0.4 mL Tubes

EPA Est. 11556-DEU-1
EPA Reg. No. 11556-XXX

Manufactured For

Bayer Corporation
Agriculture Division
Animal Health
Shawnee Mission, Kansas 66201 USA

Made in Germany



(Back Panel)

Advantage Plus® 9

Topical Solution
Fast
Effective
Multi-Stage Flea Control

Once-A-Month Topical Flea Treatment for Cats and Kittens 7 Months and Older and 9 lbs. and Under

- Available only through licensed practicing veterinarians
- Kills fleas within 12 hours
- Kills reinfesting fleas within 2 hours
- Prevents reinfestation for up to 4 weeks
- Convenient, easy to apply
- Kills adult fleas, eggs and larvae

Six 0.4 mL Tubes

(Inside Left Panel)

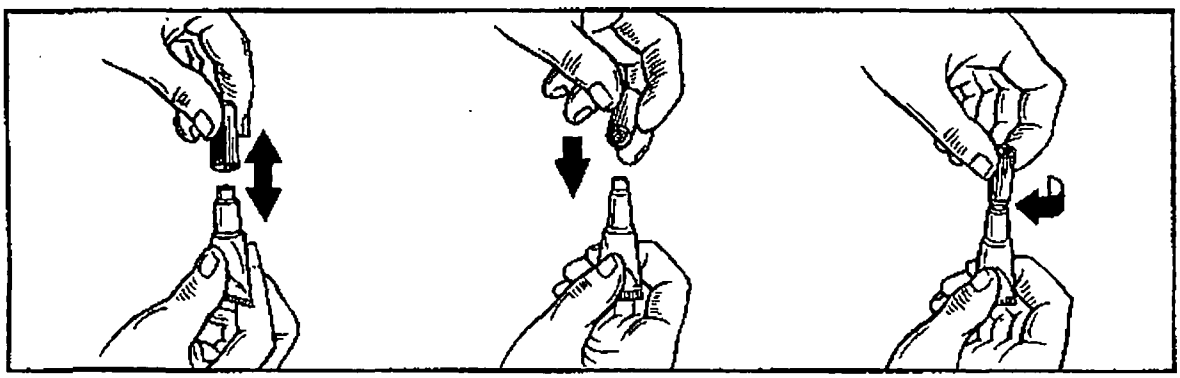
For the Prevention and Treatment of Flea Infestation on Cats and Kittens 7 Months and Older and 9 lbs and Under.

DIRECTIONS FOR USE

It is a violation of Federal Law to use this product in a manner inconsistent with its labeling.

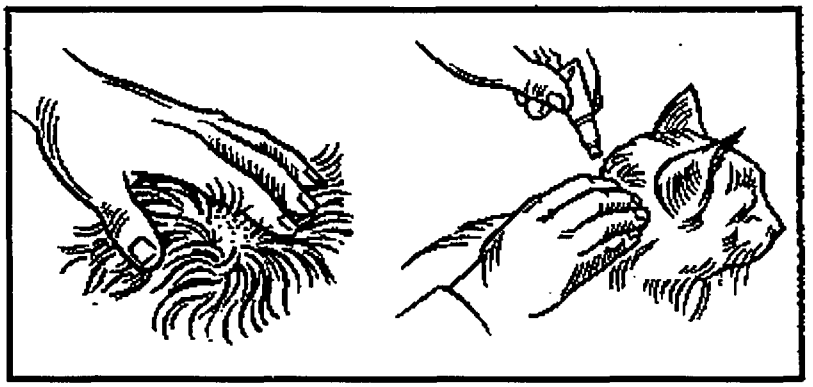
HOW TO APPLY

1. Use only on cats. Do not use on other animals.
2. Remove one applicator tube from the package.



3. Hold applicator tube in an upright position. Pull cap off tube.
4. Turn the cap around and place other end of cap back on tube.
5. Twist cap to break seal, then remove cap from tube.

6. Part the hair in the neck at the base of the skull until the skin is visible. Place the tip of the tube on the skin and squeeze the tube twice to expel the entire contents of the tube directly on the skin. Do not get this product in your pet's eyes or mouth. The product is bitter tasting and salivation may occur for a short time if the cat licks the product immediately after treatment. Treatment at the base of the skull will minimize the opportunity for the cat to lick the product.



7. Discard empty tube as described in Storage and Disposal.

(Inside Right Panel)

Advantage Plus® 9

Topical Solution

Once-a-Month topical flea treatment for cats and kittens 7 months and older and 9 lbs. and under.

The successive feeding activity of fleas on pets frequently elicits a hypersensitivity skin disorder known as flea allergy dermatitis (FAD). Treatment of pets with Advantage Plus® rapidly kills fleas and reduces the incidence of this condition.

Advantage Plus® kills 98-100% of the existing fleas on pets within 12 hours. Reinfesting fleas are killed within 2 hours with protection against further flea infestation lasting for up to four (4) weeks. Pre-existing pupae in the environment may continue to emerge for six (6) weeks or longer depending upon the climatic conditions.

Fleas, eggs and larvae in the pet's surroundings are killed following contact with an Advantage Plus® treated pet. Advantage Plus® provides multi-stage flea control effectively breaking all flea life-cycle stages for quick and lasting control of flea populations.

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Advantage Plus® remains efficacious following a shampoo treatment, swimming or after exposure to rain or sunlight.

Monthly treatments are required for optimal control and prevention of fleas.

If re-treatment becomes necessary earlier than four weeks, do not re-treat more than once weekly.

STORAGE AND DISPOSAL

Do not contaminate water, food or feed by storage or disposal.

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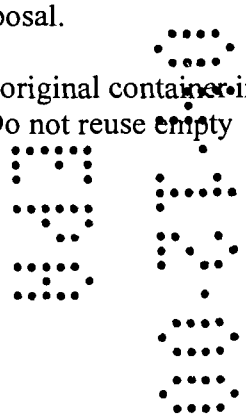

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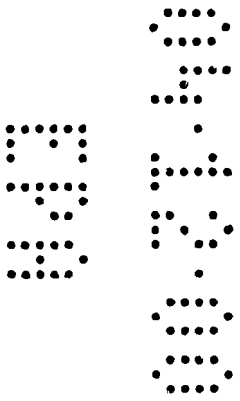

(Label on Individual Tube)

Advantage Plus®

9.10% Imidacloprid

0.46% Pyriproxyfen

0.4 mL

EPA Reg. No. 11556-XXX

CAUTION

Keep Out of Reach of Children

Read The Entire Label Before Use

BAYER

Lot No. 0000000

(Front Panel)

Advantage Plus® 9

Topical Solution

Once-A-Month Topical Flea Treatment for Cats and Kittens 7 Months and Older and 9 lbs. and Under

READ THE ENTIRE LABEL BEFORE EACH USE

For the Prevention and Treatment of Flea Infestations

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Total	100.00%

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If on skin: Wash with plenty of soap and water.

To Physician: Treat the patient symptomatically.

Six 0.4 mL Tubes

EPA Est. 11556-DEU-1
EPA Reg. No. 11556-XXX

Manufactured For

Bayer Corporation
Agriculture Division
Animal Health
Shawnee Mission, Kansas 66201 USA

Made in Germany

(Back Panel)

Advantage Plus® 9

Topical Solution
Fast
Effective
Multi-Stage Flea Control

Once-A-Month Topical Flea Treatment for Cats and Kittens 7 Months and Older and 9 lbs. and Under

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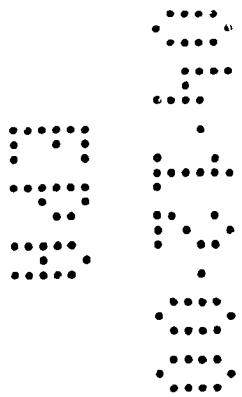

(Inside Left Panel)

For the Prevention and Treatment of Flea Infestation on Cats and Kittens 7 Months and Older and 9 lbs and Under.

DIRECTIONS FOR USE

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HOW TO APPLY

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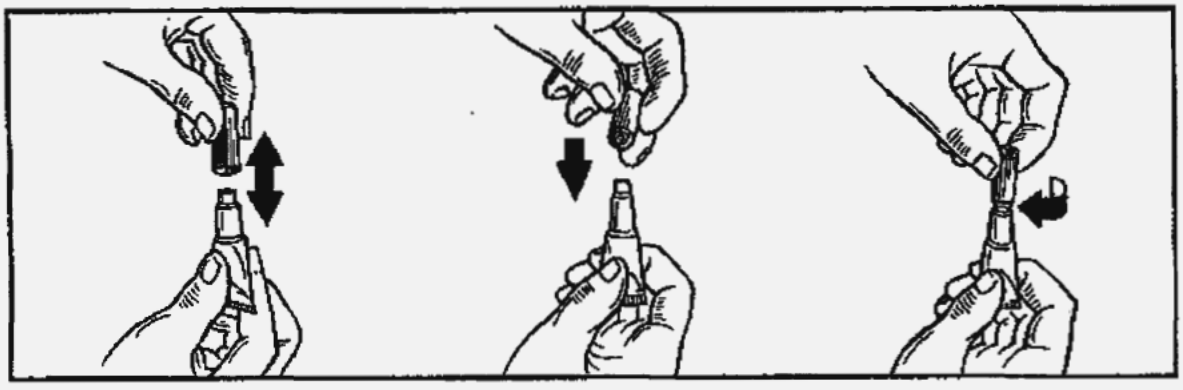

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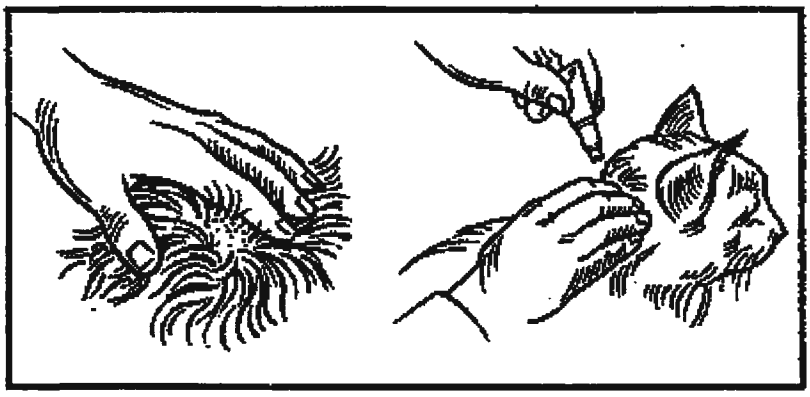

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(Inside Right Panel)

Advantage Plus® 9

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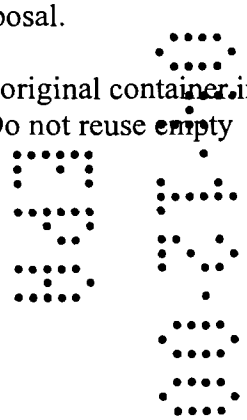

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(Label on Individual Tube)

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0.4 mL

EPA Reg. No. 11556-XXX

CAUTION

Keep Out of Reach of Children

Read The Entire Label Before Use

BAYER

Lot No. 0000000

(Front Panel)

Advantage Plus® 9

Topical Solution

Once-A-Month Topical Flea Treatment for Cats and Kittens 7 Months and Older and 9 lbs. and Under

READ THE ENTIRE LABEL BEFORE EACH USE

For the Prevention and Treatment of Flea Infestations

- Available Only Through Licensed Practicing Veterinarians
- Kills 98-100% of the Fleas on Cats Within 12 Hours
- Kills Reinfesting Fleas Within 2 Hours
- One Treatment Prevents Further Flea Infestation For Up to Four Weeks
- Kills Adult Fleas, Eggs, and Larvae
- Prevents Immature Fleas from Developing into Biting, Breeding Adults
- Provides 3-way Protection Against Fleas, Breaking Life Cycle at Egg, Larval, and Adult Stages

Active Ingredients	% By Weight
Imidacloprid; 1-[(6-Chloro-3-pyridinyl) methyl]-N-nitro-2-imidazolidinimine . .	9.10%
Pyriproxyfen; 2-[1-methyl-2-(4-phenoxyphenoxy)ethoxy] pyridine	0.46%
Inert Ingredients	90.44%
Total	100.00%

KEEP OUT OF REACH OF CHILDREN

CAUTION

See Below for First Aid and Precautionary Statements

PRECAUTIONARY STATEMENTS
HAZARDS TO HUMANS

Harmful if swallowed. Causes moderate eye irritation. Avoid contact with eyes or clothing. Wash hands thoroughly with soap and warm water after handling.

HAZARDS TO DOMESTIC ANIMALS

For external use only.
Do not use on kittens under 7 months of age.

As with any product, consult your veterinarian before using this product on debilitated, aged, pregnant or nursing animals. Individual sensitivities, while rare, may occur after using ANY pesticide product for pets. If signs persist, or become more severe, consult a veterinarian immediately. If your animal is on medication, consult your veterinarian before using this or any other product. For consumer questions call 1-800-255-6826. For medical emergencies call 1-877-258-2280.

FIRST AID

If in eyes: Hold eye open and rinse slowly and gently with water for 15-20 minutes. Remove contact lenses, if present, after the first 5 minutes, then continue rinsing eye. Call a poison control center or doctor for treatment advice.

If swallowed: Call a Poison Control Center or doctor immediately for treatment advice. Have person sip a glass of water if able to swallow. Do not induce vomiting unless told to do so by the poison control center or doctor. Do not give anything to an unconscious person.

If on skin: Wash with plenty of soap and water.

To Physician: Treat the patient symptomatically.

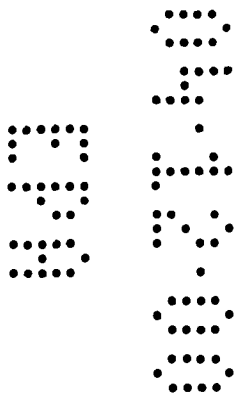
Six 0.4 mL Tubes

EPA Est. 11556-DEU-1
EPA Reg. No. 11556-XXX

Manufactured For

Bayer Corporation
Agriculture Division
Animal Health
Shawnee Mission, Kansas 66201 USA

Made in Germany



(Back Panel)

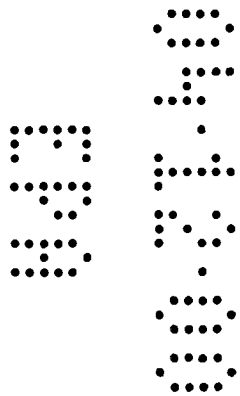
Advantage Plus® 9

Topical Solution
Fast
Effective
Multi-Stage Flea Control

Once-A-Month Topical Flea Treatment for Cats and Kittens 7 Months and Older and 9 lbs. and Under

- Available only through licensed practicing veterinarians
- Kills fleas within 12 hours
- Kills reinfesting fleas within 2 hours
- Prevents reinfestation for up to 4 weeks
- Convenient, easy to apply
- Kills adult fleas, eggs and larvae

Six 0.4 mL Tubes



(Inside Left Panel)

For the Prevention and Treatment of Flea Infestation on Cats and Kittens 7 Months and Older and 9 lbs and Under.

DIRECTIONS FOR USE

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HOW TO APPLY

1. Use only on cats. Do not use on other animals.
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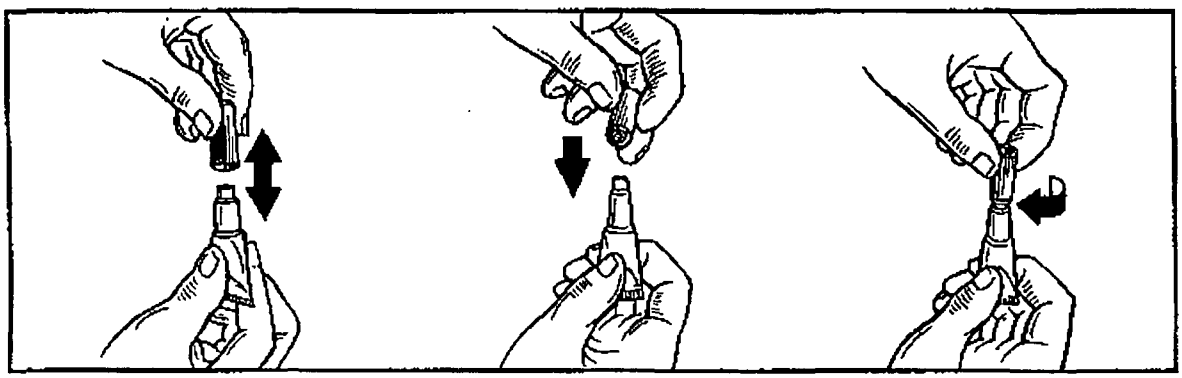
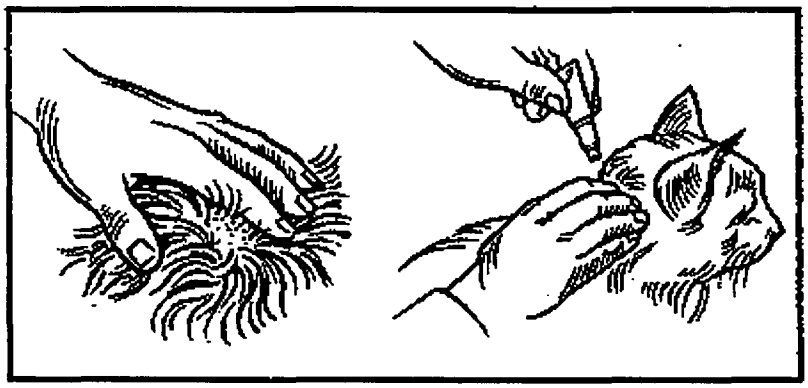


3. Hold applicator tube in an upright position. Pull cap off tube.
4. Turn the cap around and place other end of cap back on tube.
5. Twist cap to break seal, then remove cap from tube.

6. Part the hair in the neck at the base of the skull until the skin is visible. Place the tip of the tube on the skin and squeeze the tube twice to expel the entire contents of the tube directly on the skin. Do not get this product in your pet's eyes or mouth. The product is bitter tasting and salivation may occur for a short time if the cat licks the product immediately after treatment. Treatment at the base of the skull will minimize the opportunity for the cat to lick the product.



7. Discard empty tube as described in Storage and Disposal.

(Inside Right Panel)

Advantage Plus® 9

Topical Solution

Once-a-Month topical flea treatment for cats and
kittens 7 months and older and 9 lbs. and under.

The successive feeding activity of fleas on pets frequently elicits a hypersensitivity skin disorder known as flea allergy dermatitis (FAD). Treatment of pets with Advantage Plus® rapidly kills fleas and reduces the incidence of this condition.

Advantage Plus® kills 98-100% of the existing fleas on pets within 12 hours. Reinfesting fleas are killed within 2 hours with protection against further flea infestation lasting for up to four (4) weeks. Pre-existing pupae in the environment may continue to emerge for six (6) weeks or longer depending upon the climatic conditions.

Fleas, eggs and larvae in the pet's surroundings are killed following contact with an Advantage Plus® treated pet. Advantage Plus® provides multi-stage flea control effectively breaking all flea life-cycle stages for quick and lasting control of flea populations.

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Advantage Plus® remains efficacious following a shampoo treatment, swimming or after exposure to rain or sunlight.

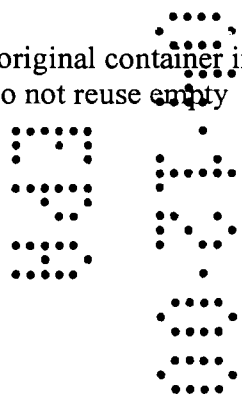
Monthly treatments are required for optimal control and prevention of fleas.

If re-treatment becomes necessary earlier than four weeks, do not re-treat more than once weekly.

STORAGE AND DISPOSAL

Do not contaminate water, food or feed by storage or disposal.

Storage: Store in a cool, dry place. **Pesticide Disposal**: Securely wrap original container in several layers of newspaper and discard in trash. **Container Disposal**: Do not reuse empty container. Wrap container and put in trash.



LIMITED WARRANTY AND LIMITATION OF DAMAGES

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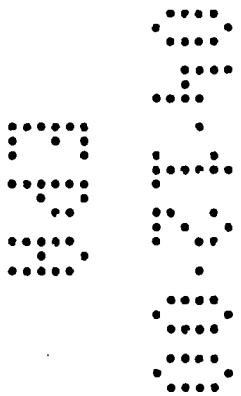

(Label on Individual Tube)

Advantage Plus®

9.10% Imidacloprid

0.46% Pyriproxyfen

0.4 mL

EPA Reg. No. 11556-XXX

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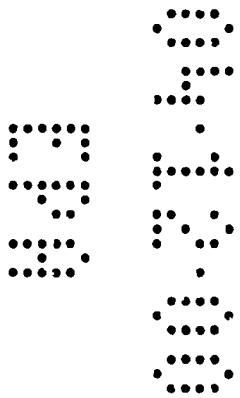

(Front Panel)

Advantage Plus® 9

Topical Solution

Once-A-Month Topical Flea Treatment for Cats and Kittens 7 Months and Older and 9 lbs. and Under

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Six 0.4 mL Tubes

EPA Est. 11556-DEU-1
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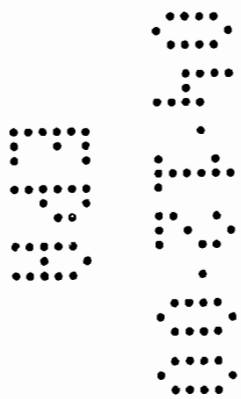

(Inside Left Panel)

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DIRECTIONS FOR USE

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HOW TO APPLY

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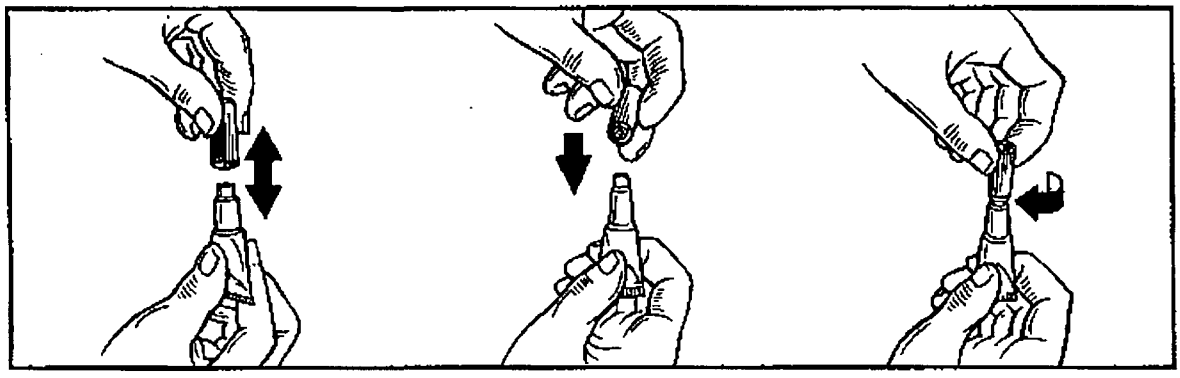

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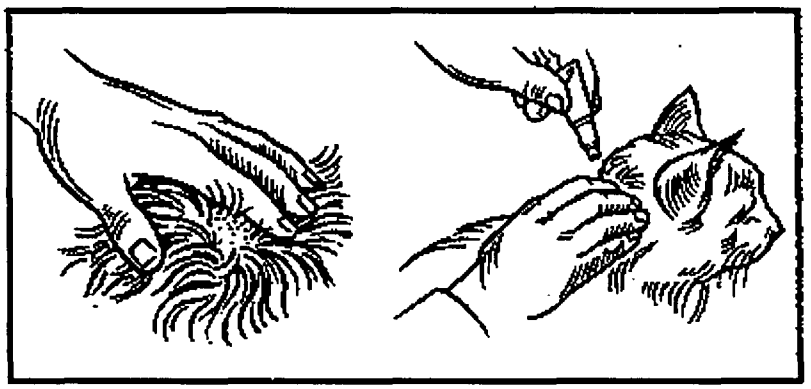

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(Inside Right Panel)

Advantage Plus® 9

Topical Solution

Once-a-Month topical flea treatment for cats and
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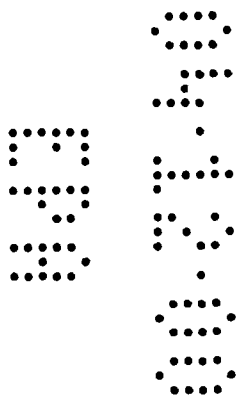

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0.4 mL

EPA Reg. No. 11556-XXX

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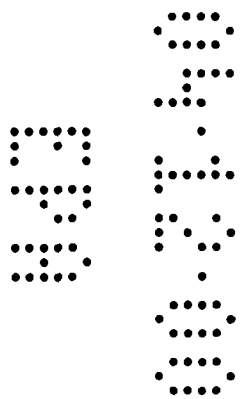

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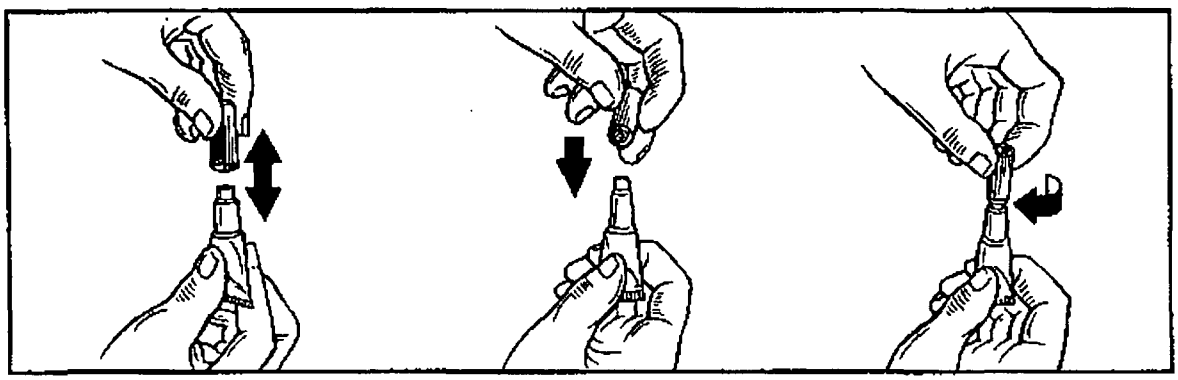

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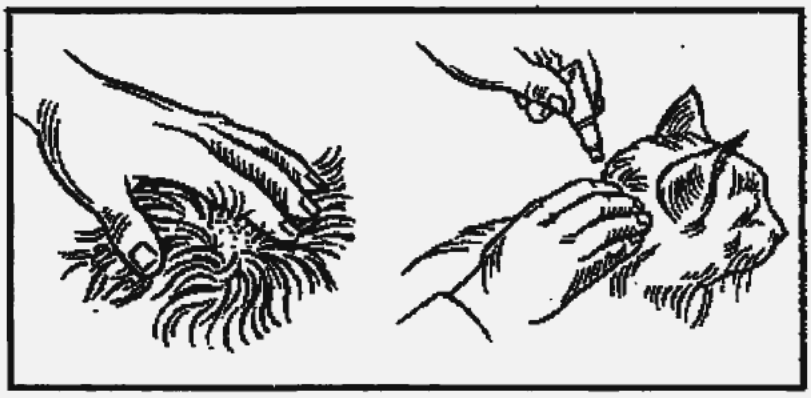

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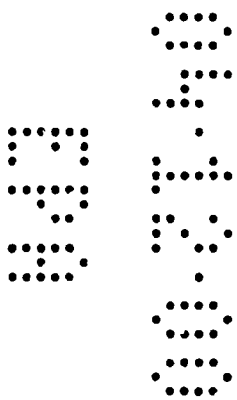

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Pages 214-216 Confidential Statement of Formula may be entitled to confidential treatment